eVENUS

HENGRUI

FRESENIUS KABI

DEFENDANTS' CLOSING STATEMENT

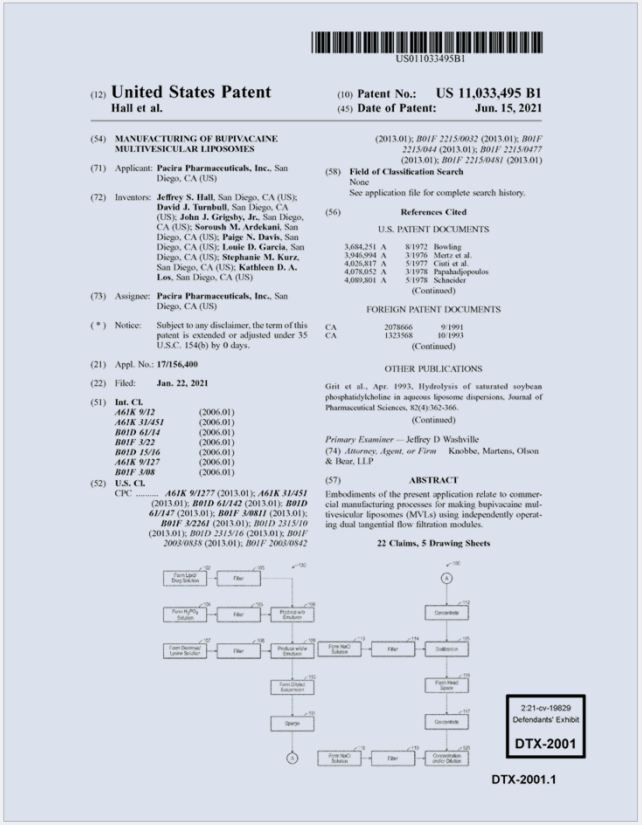
May 7, 2024

Case Nos. 2:21-cv-19829 & 2:22-cv-00718 (consolidated)

DISTRICT OF NEW JERSEY

Hon. Madeline Cox Arleo

’495 Patent, Claims 1, 3, 5, and 7



US011033495B1

(12) **United States Patent**
Hall et al.

(10) **Patent No.: US 11,033,495 B1**
(45) **Date of Patent: Jun. 15, 2021**

(54) **MANUFACTURING OF BUPIVACAINE MULTIVESICULAR LIPOSOMES**

(71) Applicant: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(72) Inventors: **Jeffrey S. Hall**, San Diego, CA (US); **David J. Turnbull**, San Diego, CA (US); **John J. Grigsby, Jr.**, San Diego, CA (US); **Soroush M. Ardekani**, San Diego, CA (US); **Paige N. Davis**, San Diego, CA (US); **Louie D. Garcia**, San Diego, CA (US); **Stephanie M. Kurz**, San Diego, CA (US); **Kathleen D. A. Los**, San Diego, CA (US)

(73) Assignee: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/156,400**

(22) Filed: **Jan. 22, 2021**

(51) **Int. Cl.**
A61K 9/12 (2006.01)
A61K 31/451 (2006.01)
B01D 61/14 (2006.01)
B01F 3/22 (2006.01)
B01D 15/16 (2006.01)
A61K 9/127 (2006.01)
B01F 3/08 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 9/1277*** (2013.01); ***A61K 31/451*** (2013.01); ***B01D 61/142*** (2013.01); ***B01D 61/147*** (2013.01); ***B01F 3/0811*** (2013.01); ***B01F 3/2261*** (2013.01); ***B01D 2315/10*** (2013.01); ***B01D 2315/16*** (2013.01); ***B01F 2003/0838*** (2013.01); ***B01F 2003/0842*** (2013.01); ***B01F 2215/0032*** (2013.01); ***B01F 2215/044*** (2013.01); ***B01F 2215/0477*** (2013.01); ***B01F 2215/0481*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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3,684,251 A 8/1972 Bowling
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4,026,817 A 5/1977 Ciuti et al.
4,078,052 A 3/1978 Papahadjopoulos
4,089,801 A 5/1978 Schneider
(Continued)

FOREIGN PATENT DOCUMENTS

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CA 1323568 10/1993
(Continued)

OTHER PUBLICATIONS

Grit et al., Apr. 1993, Hydrolysis of saturated soybean phosphatidylcholine in aqueous liposome dispersions, Journal of Pharmaceutical Sciences, 82(4):362-366.
(Continued)

Primary Examiner — Jeffrey D Washville
(74) *Attorney, Agent, or Firm* Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

Embodiments of the present application relate to commercial manufacturing processes for making bupivacaine multivesicular liposomes (MVLs) using independently operating dual tangential flow filtration modules.

22 Claims, 5 Drawing Sheets

2:21-cv-19829
Defendants' Exhibit
DTX-2001

DTX-2001.1

What is claimed is:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:

(a) mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;

(b) mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;

(c) removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;

(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;

(e) exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and

(f) further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;

wherein all steps are carried out under aseptic conditions; and

wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month.

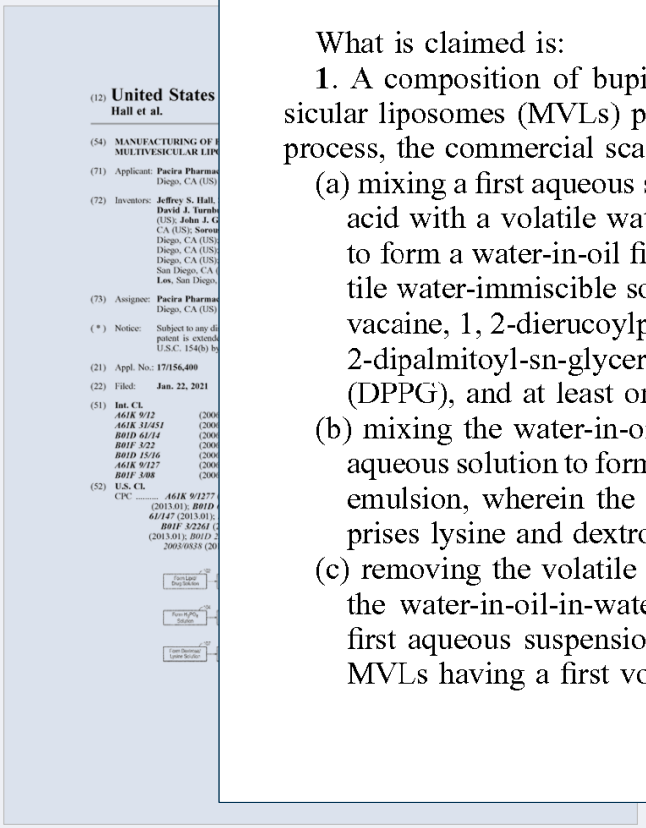
3. The composition of claim 1, wherein the erucic acid concentration in the composition is about 38 μg/mL or less after the composition is stored at 25° C. for two months.

5. The composition of claim 1, wherein the erucic acid concentration in the composition is about 54 μg/mL or less after the composition is stored at 25° C. for three month.

7. The composition of claim 1, wherein the erucic acid concentration in the composition is about 99 μg/mL or less after the composition is stored at 25° C. for six months.

JTX-4121.20-21, claims 1, 3, 5, 7

’495 Patent, Claim 1



What is claimed is:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:

(a) mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;

(b) mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;

(c) removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;

(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;

(e) exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and

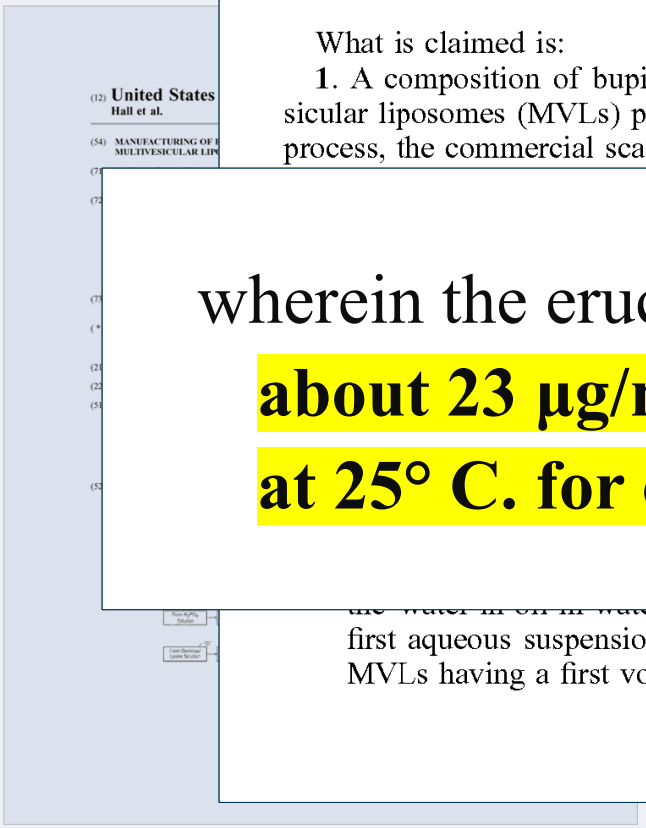
(f) further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;

wherein all steps are carried out under aseptic conditions; and

wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month.

JTX-4121.20-21, claim 1

’495 Patent, Claim 1



What is claimed is:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:

first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;

(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of

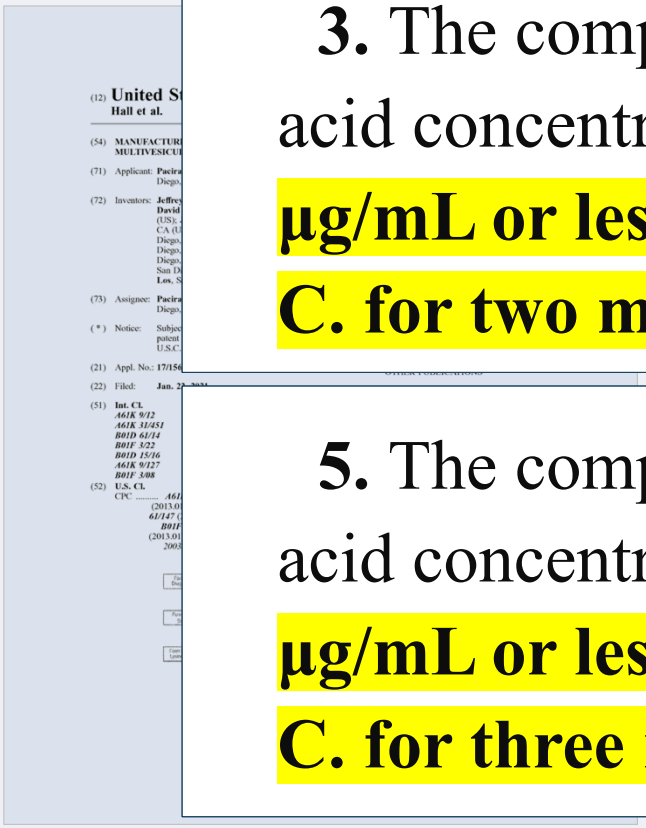
and

wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month.

wherein the erucic acid concentration in the composition is **about 23 μg/mL or less after the composition is stored at 25° C. for one month**.

JTX-4121.20-21, claim 1

’495 Patent, Claims 3 and 5

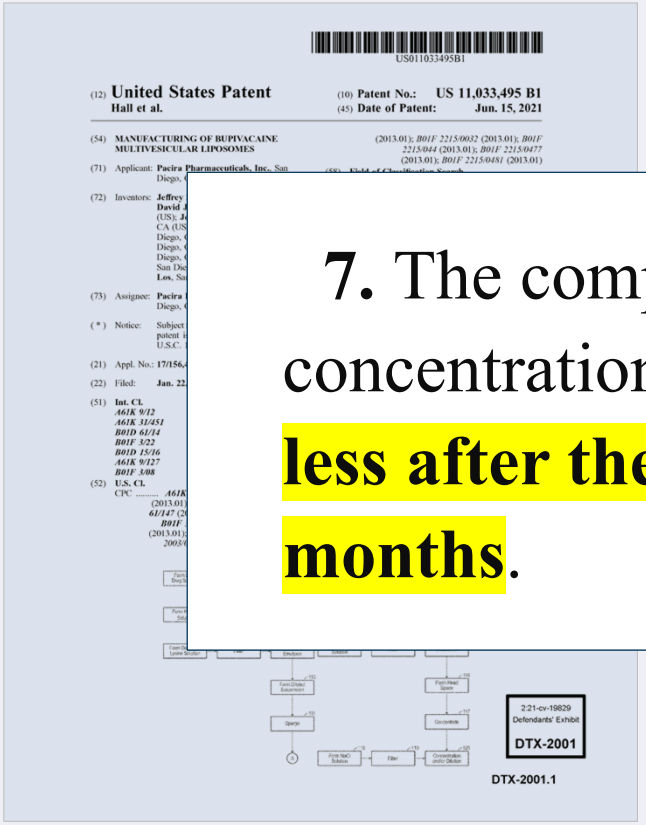


3. The composition of claim 1, wherein the erucic acid concentration in the composition is **about 38 µg/mL or less after the composition is stored at 25° C. for two months**.

5. The composition of claim 1, wherein the erucic acid concentration in the composition is **about 54 µg/mL or less after the composition is stored at 25° C. for three month**.

JTX-4121.21, claims 3, 5

’495 Patent, Claim 7


US011033495B1

(12) United States Patent
Hall et al.

(10) Patent No.: US 11,033,495 B1
(45) Date of Patent: Jun. 15, 2021

(54) MANUFACTURING OF BUPIVACAINE MULTIVESICULAR LIPOSOMES

(71) Applicant: Pacira Pharmaceuticals, Inc., San Diego,

(72) Inventors: Jeffrey David J. (US); J. CA (US); Diego, Diego, Diego, San Die Los, Sa

(73) Assignee: Pacira Diego,

(*) Notice: Subject patent i U.S.C.

(21) Appl. No.: 17/156,

(22) Filed: Jan. 22,

(51) Int. Cl.
A61K 9/12
A61K 31/451
B01D 61/14
B01F 3/22
B01D 15/16
A61K 9/127
B01F 3/08

(52) U.S. Cl.
CPC .....

(2013.01); B01F 2215/0032 (2013.01); B01F 2215/044 (2013.01); B01F 2215/0477 (2013.01); B01F 2215/0481 (2013.01)

2:21-cv-19829
Defendants' Exhibit
DTX-2001

DTX-2001.1

7. The composition of claim 1, wherein the erucic acid concentration in the composition is **about 99 µg/mL or less after the composition is stored at 25° C. for six months**.

JTX-4121.21, claim 7

Erucic Acid Stability Data in the ’495 Patent

“New Process”

Old or “Current Commercial Process”

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

JTX-4121.19, Table 1A at 20:47-67

Erucic Acid Stability Data in the '495 Patent

Months Storage at 25°C	"New" Process Average in Patent	"Old" Process Average in Patent
1 month	22.7 µg/mL	n/a
2 months	37.3 µg/mL	38.7 µg/mL
3 months	53.0 µg/mL	55.4 µg/mL
6 months	98.7 µg/mL	113.1 µg/mL

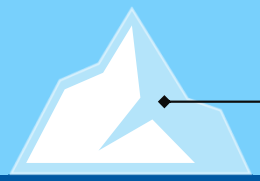
See JTX-4121.19, Table 1A at 20:47-67

Claims to the Erucic Acid Concentration

Months Storage at 25 °C	"New" Process Average in Patent	Claimed Erucic Acid Concentration	"Old" Process Average in Patent
1 month	22.7 µg/mL	≤ ~23 µg/mL (Claim 1)	n/a
2 months	37.3 µg/mL	≤ ~38 µg/mL (Claim 3)	38.7 µg/mL
3 months	53.0 µg/mL	≤ ~54 µg/mL (Claim 5)	55.4 µg/mL
6 months	98.7 µg/mL	≤ ~99 µg/mL (Claim 7)	113.1 µg/mL

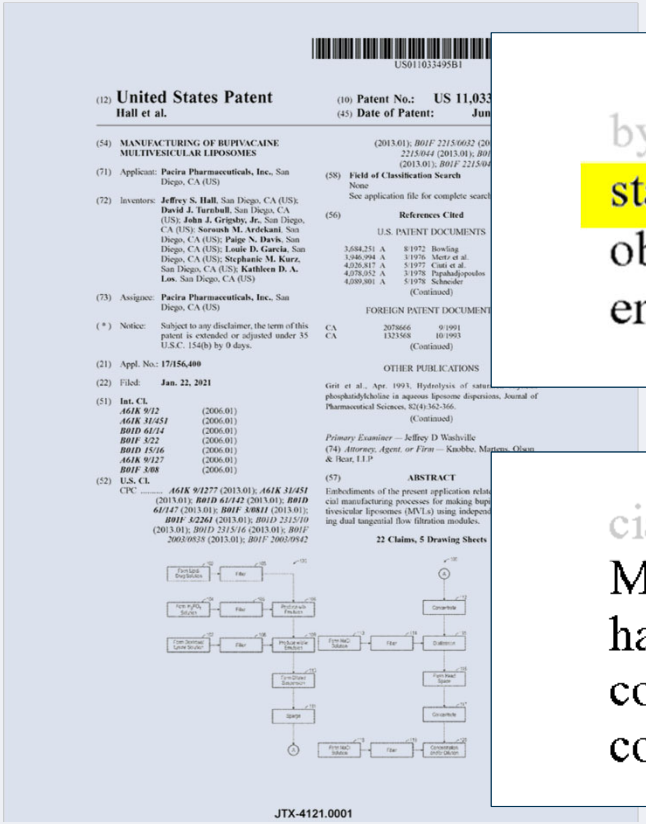
See JTX-4121.19, Table 1A at 20:47-67;
see also id. at -.20-21, claims 1, 3, 5, 7

Pacira's 45-L Data



'495 Patent
(JTX-4121)

The ’495 Patent – Stability



US011033495B1

(12) **United States Patent**
Hall et al.

(10) **Patent No.: US 11,033**
(45) **Date of Patent: Jun**

(54) **MANUFACTURING OF BUPIVACAINE MULTIVESICULAR LIPOSOMES**

(71) Applicant: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(72) Inventors: **Jeffrey S. Hall**, San Diego, CA (US); **David J. Turnbull**, San Diego, CA (US); **John J. Grigsby, Jr.**, San Diego, CA (US); **Soroush M. Ardekani**, San Diego, CA (US); **Paige N. Davis**, San Diego, CA (US); **Louie D. Garcia**, San Diego, CA (US); **Stephanie M. Kurz**, San Diego, CA (US); **Kathleen D. A. Los**, San Diego, CA (US)

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(58) **Field of Classification Search**
None
See application file for complete search

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,684,251 A 8/1972 Bowling
3,946,994 A 3/1976 Mertz et al.
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4,078,052 A 3/1978 Papahadjopoulos
4,089,801 A 5/1978 Schneider
(Continued)

FOREIGN PATENT DOCUMENT

CA 2078666 9/1991
CA 1323568 10/1993
(Continued)

OTHER PUBLICATIONS

Grit et al., Apr. 1993, Hydrolysis of satu... phosphatidylcholine in aqueous liposome dispersions, Journal of Pharmaceutical Sciences, 82(4):362-366.
(Continued)

Primary Examiner — Jeffrey D Washville
(74) *Attorney, Agent, or Firm* — Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

Embodiments of the present application relate... cial manufacturing processes for making bupi... tivesicular liposomes (MVLs) using independ... ing dual tangential flow filtration modules.

22 Claims, 5 Drawing Sheets

JTX-4121.0001

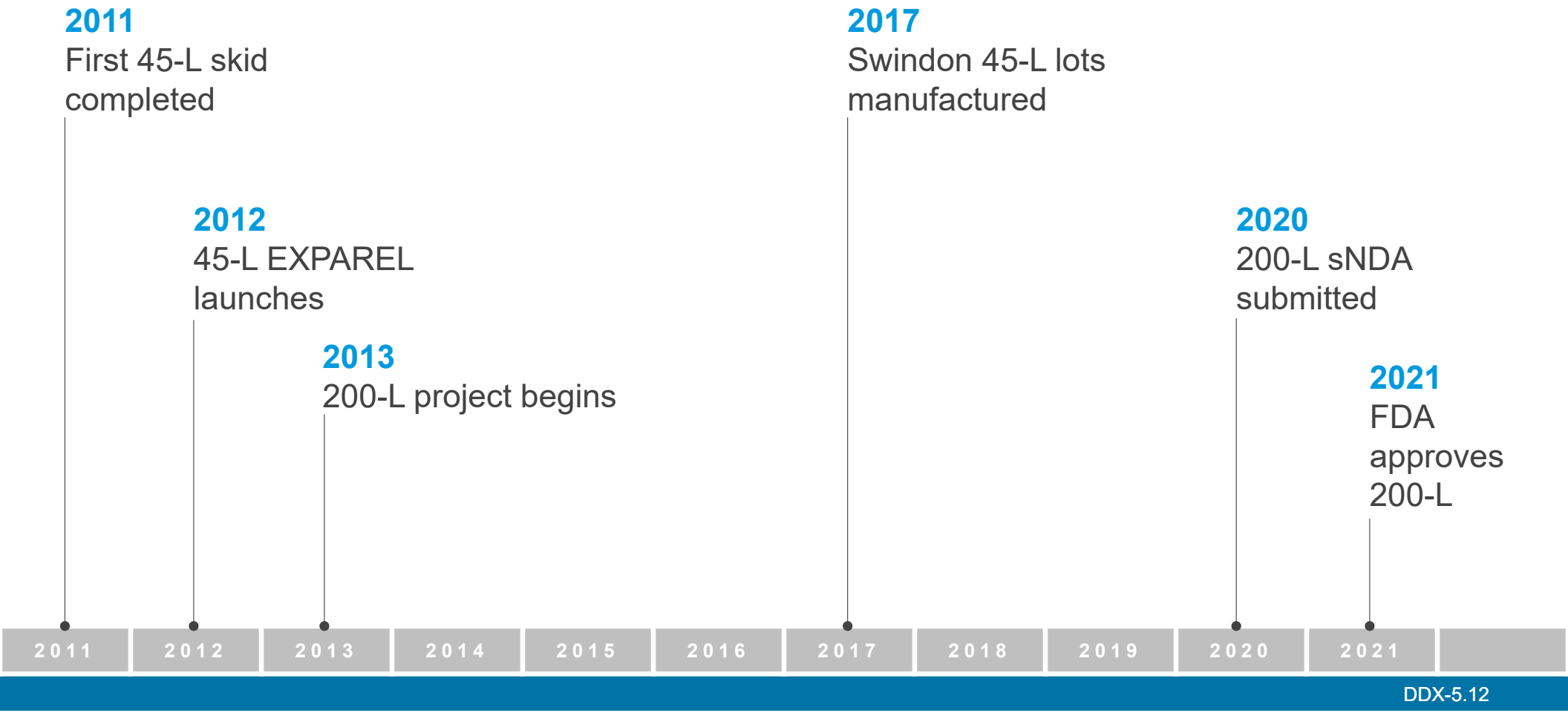
by the existing commercial process. The improved lipid stability (as indicated by the erucic acid concentration) observed in the bupivacaine MVLs prepared by the presently described process was surprisingly unexpected.

JTX-4121.21 at 51-55

cial Exparel® product. It was observed that the bupivacaine MVL particles produced by the process described herein have lower lipid hydrolysis byproducts compared to the commercial Exparel® product under the same incubation condition. In addition, the bupivacaine MVL particles pro-

JTX-4121.16 at 13:51-55

EXPAREL Timeline



Mr. Molloy: In 2020, Pacira Was About to Lose Patent Protection for EXPAREL

Anthony Molloy

PACIRA PHARMACEUTICALS, INC.

Q. [A]t the end of 2020, there was only one patent listed in the Orange Book for Exparel, correct?

A. That's correct.

***

Q. And the patent was set to expire December 24th, 2021, right?

A. That's true.

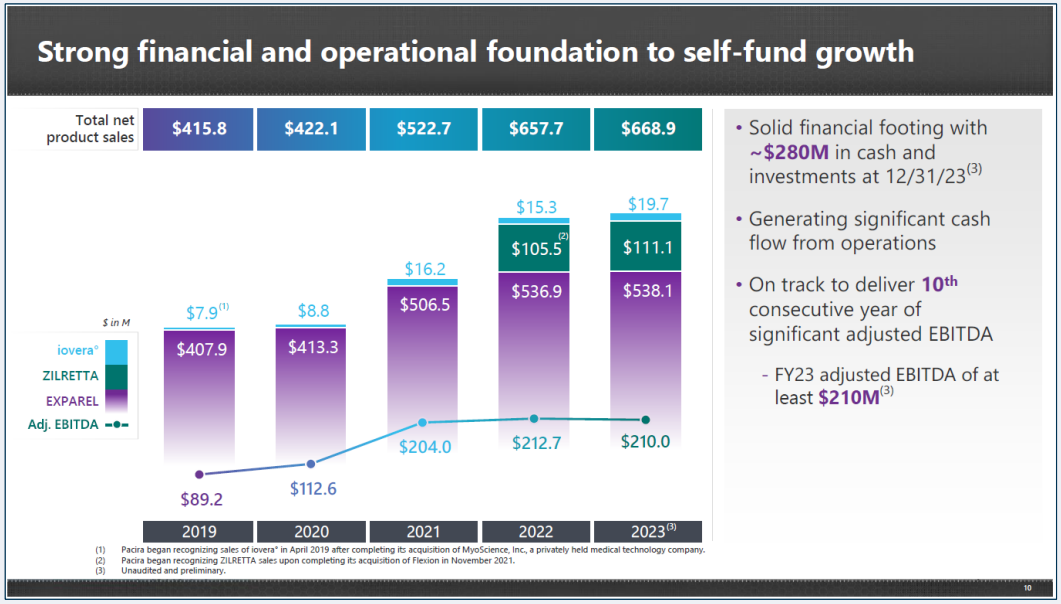
***

Q. If Pacira did not get any additional patents that covered Exparel before December 24th, 2021, Pacira would have no patents left in the Orange Book covering that product, correct?

A. Yes.

Tr. 339:6-8, 14-16, 20-23 (Molloy)

In 2020, EXPAREL Was "Pacira's Most Important Product"



DTX-3116.10

Q. Now, Exparel was an important product for Pacira at the end of 2020, correct?

A. Agree, yes.

Q. It was Pacira's most important product; is that fair?

A. Yes.

* * *

Q. And in 2020, Pacira reported $422.1 million in total net product sales, correct?

A. Yes.

Q. And the purple represents the sales that came from Exparel?

A. That's correct.

Q. And it was $413.3 million, right?

A. That's true.

Q. And will you trust my math if I say that's in excess of 95 percent?

A. I will.

Q. In fact today even, Pacira gets the vast majority of its revenue from Exparel, correct?

A. Yes.

Q. Almost 85 percent, right?

A. I'll trust your math again.

Tr. 340:5-9, 341:5-20 (Molloy)

Mr. Molloy: Pacira Knew It Needed a "New" Product Patent

Anthony Molloy

PACIRA PHARMACEUTICALS, INC.

Q. And so for Pacira to be able to list this patent in the Orange Book, you had to identify some difference between the product made by the new process and the product made by the old process, right?

A. Yes.

Q. If the products were the same, the patent doesn't go in the Orange Book, right?

A. If the products were the same, you wouldn't get the patent.

Q. Well, you'd get a patent on the manufacturing process, right?

A. Oh, I'm – I'm sorry. You're correct. I'm sorry.

Q. The only way you can get a patent on a manufacturing process that you can list in the Orange Book is if the product that comes from that process is different than the prior product, right?

A. That's right.

Tr. 358:23-359:14 (Molloy)

Ms. Los: No Role in Scale-Up

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. Ms. Los, are you aware that there was recently a 200-liter scale-up of the EXPAREL manufacturing process?

A. Yes, I'm aware of that.

Q. Generally speaking, what was your role, if any, in that scale-up?

A. My personal role in that scale-up? I have no role in that scale-up.

JTX-4289.8 (Los Tr. 51:7-9, 51:11, 51:12-15)

Ms. Los: 50-60% of Time Spent on Patent Work

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. Ms. Los, over the past two years, what percentage of your time would you say that you've spent on developing patent strategies and writing patent documents?

A. I would say more like 50 to 60 percent.

JTX-4289.6 (Los Tr. 47:3-6, 47:8)

Ms. Los: Reports to Pacira's Legal Team

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. Who do you report to as the director of formulation development?

A. Most recently, I report directly to Elena McDermott.

Q. Who is Elena McDermott?

A. She is a member of the legal team, Pacira's internal legal team.

JTX-4289.4 (Los Tr. 35:14-20)

Ms. Los: Aware that EXPAREL Was Pacira's Largest Product

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. So, Ms. Los, is it your testimony here today that you have no idea whether or not EXPAREL is the largest product that Pacira sells in terms of sales?

A. Well, I have – I – I believe it probably is but I can't verify that because I don't know for sure.

JTX-4289.7 (Los Tr. 49:10-16)

Ms. Los: Aware of Pacira's Orange Book Patent

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. As of 2020, Ms. Los, were you aware of whether Pacira had Orange Book patents listed for EXPAREL?

A. Yes, I was aware of that.

Q. Did Pacira have Orange Book patents listed for EXPAREL as of 2020?

A. Yes.

JTX-4289.11-12 (Los Tr. 65:15-21)

Ms. Los: Knew Pacira's Orange Book Patent Would Soon Expire

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. As of 2020, were you aware of when those patents were going to expire?

A. Yes, I was aware.

Q. When were they going to expire?

A. Sorry. My years start to get – I believe it was at the end of 2021.

JTX-4289.12 (Los Tr. 65:22-23, 65:25-66:3)

Ms. Los: Better for Pacira to Have Orange Book Patents

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. And I think as we previously mentioned, Ms. Los, having zero Orange Book patents with all things being equal have been bad for Pacira?

A. Well, it's my understanding that it would be more favorable for Pacira to have that patent.

JTX-4289.12 (Los Tr. 66:4-6, 66:16-18)

Dr. Dai: Prosecuting Pacira's Patents Since 2012

Dr. Jane Dai

Q. Fair to say that you have prosecuted somewhere between 200 and 500 patents over the course of your career?

A. Yeah, that's probably correct.

***

Q. Dr. Dai, one of your clients at Knobbe is Pacira Pharmaceuticals; correct?

A. That's correct.

Q. When did you start working with Pacira?

A. Maybe 2012, if I remember correctly.

Q. Fair to say that you have prosecuted somewhere between 30 and 50 patent applications for Pacira?

A. That's – that's probably true.

JTX-4288.2-3 (Dai Tr. 27:16-19, 35:19-23, 36:20-22, 36:25)

Dr. Dai: Drafted and Reviewed the ’495 Patent

Dr. Jane Dai

Q. What was your role in drafting the ’495 patent?

A. I supervised the associate who draft the application.

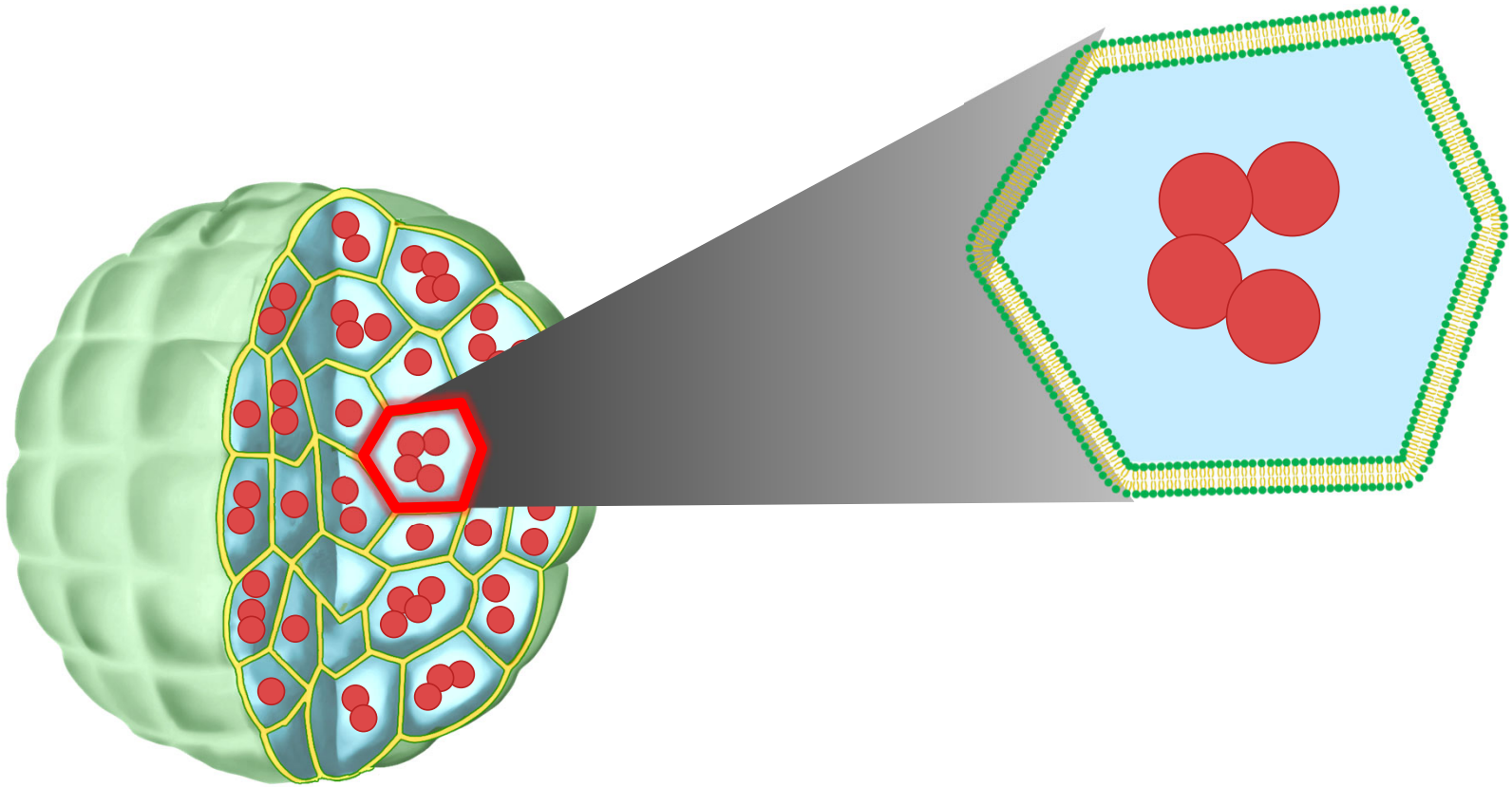
***

Q. When you say you reviewed the work product, does that mean that you reviewed the application for the ’495 patent before it was filed?

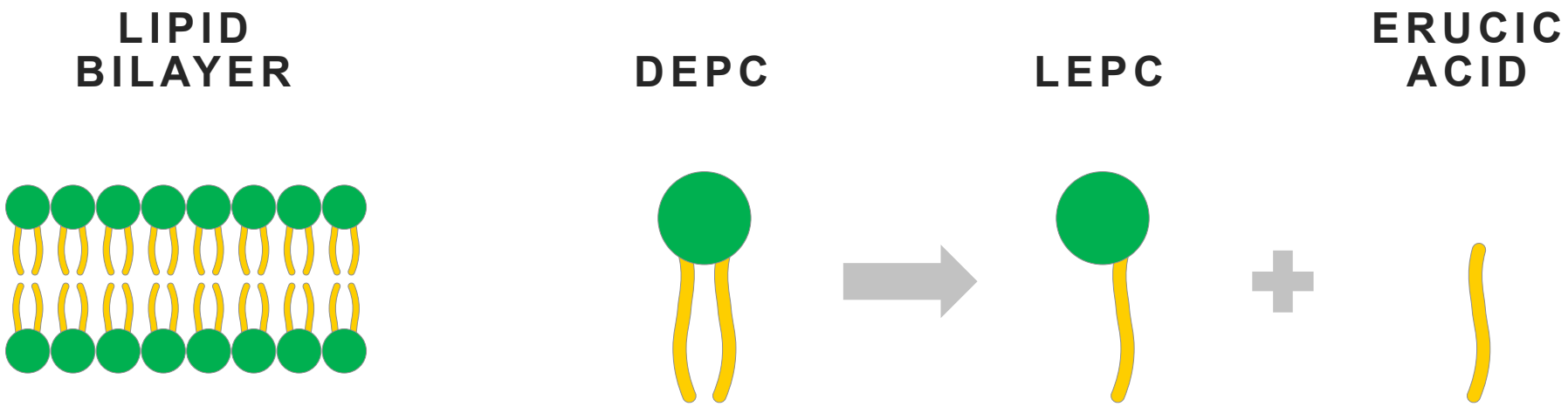
A. Yes.

JTX-4288.4 (Dai Tr. 58:16-17, 59:1-2, 59:10-13)

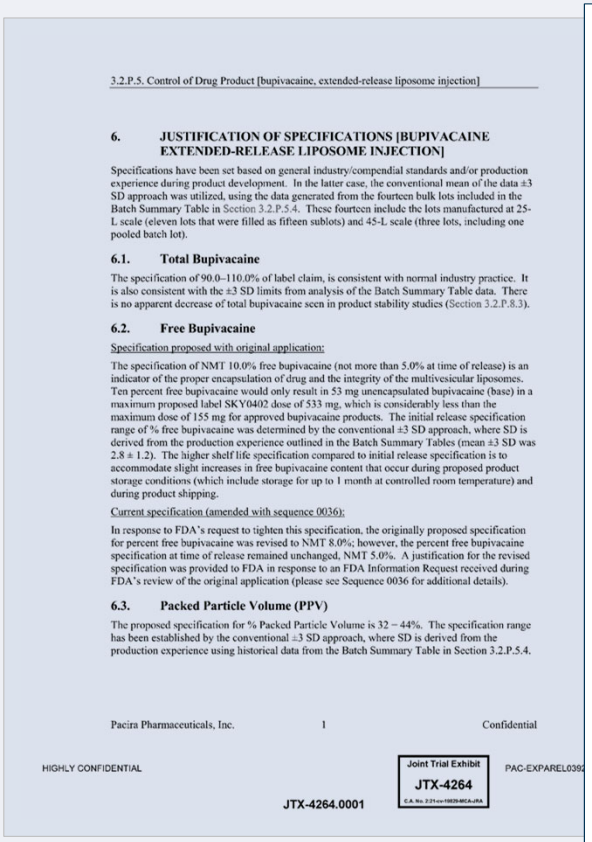
Multivesicular Liposomes



Liposome Degradation



Erucic Acid Values Up to 310 µg/mL Maintain Product Performance



3.2.P.5. Control of Drug Product [bupivacaine, extended-release liposome injection]

6. JUSTIFICATION OF SPECIFICATIONS [BUPIVACAINE EXTENDED-RELEASE LIPOSOME INJECTION]

Specifications have been set based on general industry/compendial standards and/or production experience during product development. In the latter case, the conventional mean of the data ±3 SD approach was utilized, using the data generated from the fourteen bulk lots included in the Batch Summary Table in Section 3.2.P.5.4. These fourteen include the lots manufactured at 25-L scale (eleven lots that were filled as fifteen sublots) and 45-L scale (three lots, including one pooled batch lot).

6.1. Total Bupivacaine

The specification of 90.0–110.0% of label claim, is consistent with normal industry practice. It is also consistent with the ±3 SD limits from analysis of the Batch Summary Table data. There is no apparent decrease of total bupivacaine seen in product stability studies (Section 3.2.P.8.3).

6.2. Free Bupivacaine

Specification proposed with original application:

The specification of NMT 10.0% free bupivacaine (not more than 5.0% at time of release) is an indicator of the proper encapsulation of drug and the integrity of the multivesicular liposomes. Ten percent free bupivacaine would only result in 53 mg unencapsulated bupivacaine (base) in a maximum proposed label SKY0402 dose of 533 mg, which is considerably less than the maximum dose of 155 mg for approved bupivacaine products. The initial release specification range of % free bupivacaine was determined by the conventional ±3 SD approach, where SD is derived from the production experience outlined in the Batch Summary Tables (mean ±3 SD was 2.8 ± 1.2). The higher shelf life specification compared to initial release specification is to accommodate slight increases in free bupivacaine content that occur during proposed product storage conditions (which include storage for up to 1 month at controlled room temperature) and during product shipping.

Current specification (amended with sequence 0036):

In response to FDA's request to tighten this specification, the originally proposed specification for percent free bupivacaine was revised to NMT 8.0%; however, the percent free bupivacaine specification at time of release remained unchanged, NMT 5.0%. A justification for the revised specification was provided to FDA in response to an FDA Information Request received during FDA's review of the original application (please see Sequence 0036 for additional details).

6.3. Packed Particle Volume (PPV)

The proposed specification for % Packed Particle Volume is 32 – 44%. The specification range has been established by the conventional ±3 SD approach, where SD is derived from the production experience using historical data from the Batch Summary Table in Section 3.2.P.5.4.

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Joint Trial Exhibit JTX-4264

JTX-4264.0001

JTX-4264.5

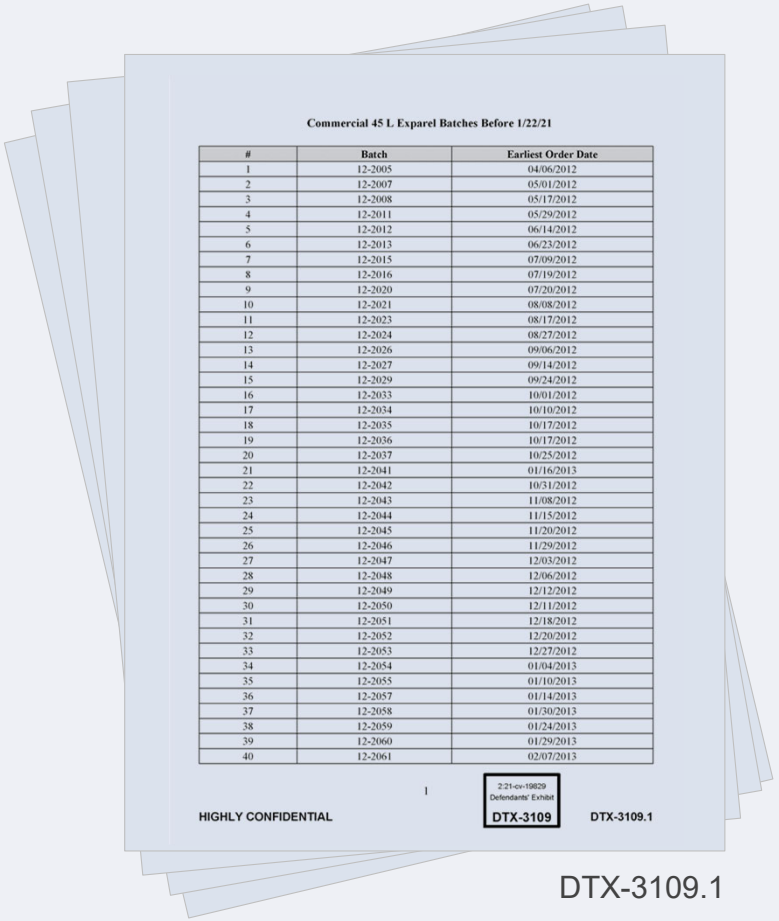
6.9. Erucic Acid

Erucic acid is selected as a marker for monitoring degradation of DEPC and other lipids in SKY0402. The specification of erucic acid is NMT 310 µg/mL (or 10.0% nominal DEPC content assuming hydrolysis of one acyl chain) and NMT 155 µg/mL (or 5.0% nominal DEPC) at time of release. DEPC is the major phospholipid excipient in the formulation, and is prone to hydrolysis to erucic acid and lyso-DEPC. Lyso-DEPC may further undergo hydrolysis to form erucic acid and glycero-3-phosphocholine. Therefore, monitoring of erucic acid represents a better and more robust indicator of DEPC degradation.

In stability studies (Section 3.2.P.8.3.3.2), erucic acid has been observed at levels up to approximately 310 µg/mL at the 24-month time point (10% degradation expressed as percent of nominal DEPC equivalent) in some earlier batches of SKY0402 (05-2502, 05-2503, 06-2502 and 06-2503). This level of erucic acid was observed to have no affect on the in vitro release of SKY0402. Studies performed with aged liposome dispersions containing lysolipids as products of hydrolytic decomposition of constituent phospholipids indicate that up to 15 % degradation of phospholipid to its respective fatty acid moiety and lysophospholipid does not significantly alter the bilayer permeability[1]. In addition, the PK of the SKY0402 lot 06-2503 with approximately 310 µg/mL of erucic acid was evaluated in a Phase 1 clinical study along with low erucic acid content lots (44 – 55 µg/mL) (See Section 2.7.4.1.1.1, SKY0402-C-108). All lots showed comparable pharmacokinetic profiles, demonstrating that product with erucic acid values up to 310 µg/mL will maintain product performance.

Based on this, a specification of NMT 310 µg/mL erucic acid in SKY0402 is justified. The initial release specification limit of NMT 155 µg/mL erucic acid (5% nominal DEPC degradation) is also proposed.

Over 2,500 45-L Batches Manufactured and Sold Before Priority Date



Commercial 45 L Exparel Batches Before 1/22/21

#	Batch	Earliest Order Date
1	12-2005	04/06/2012
2	12-2007	05/01/2012
3	12-2008	05/17/2012
4	12-2011	05/29/2012
5	12-2012	06/14/2012
6	12-2013	06/23/2012
7	12-2015	07/09/2012
8	12-2016	07/19/2012
9	12-2020	07/20/2012
10	12-2021	08/08/2012
11	12-2023	08/17/2012
12	12-2024	08/27/2012
13	12-2026	09/06/2012
14	12-2027	09/14/2012
15	12-2029	09/24/2012
16	12-2033	10/01/2012
17	12-2034	10/10/2012
18	12-2035	10/17/2012
19	12-2036	10/17/2012
20	12-2037	10/25/2012
21	12-2041	01/16/2013
22	12-2042	10/31/2012
23	12-2043	11/08/2012
24	12-2044	11/15/2012
25	12-2045	11/20/2012
26	12-2046	11/29/2012
27	12-2047	12/03/2012
28	12-2048	12/06/2012
29	12-2049	12/12/2012
30	12-2050	12/11/2012
31	12-2051	12/18/2012
32	12-2052	12/20/2012
33	12-2053	12/27/2012
34	12-2054	01/04/2013
35	12-2055	01/10/2013
36	12-2057	01/14/2013
37	12-2058	01/30/2013
38	12-2059	01/24/2013
39	12-2060	01/29/2013
40	12-2061	02/07/2013

1

2:21-cv-19829 Defendants' Exhibit DTX-3109

HIGHLY CONFIDENTIAL DTX-3109.1

DTX-3109.1

Q. Dr. Schwendeman, how many batches of prior art Exparel product did Pacira sell before the ’495 patent’s priority date?

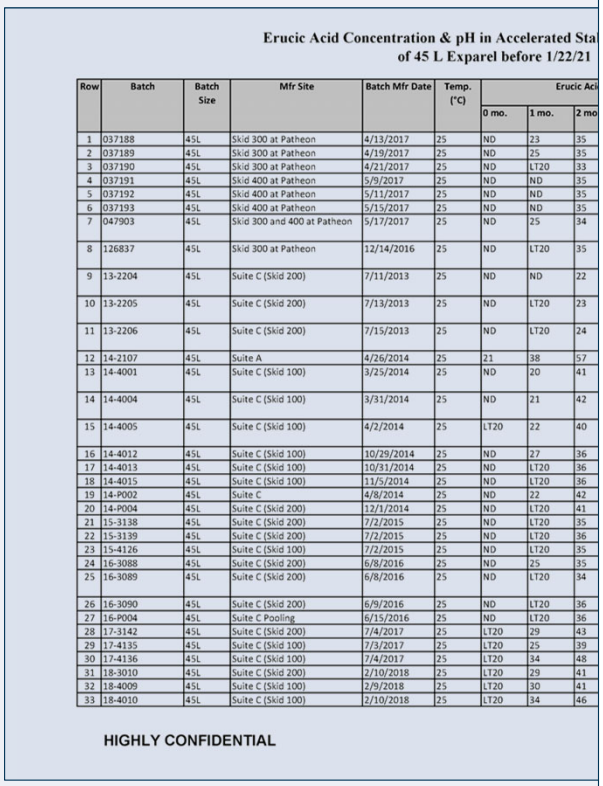
A. I believe it was about 25 – 2500, close to 2600 batches.

Q. Did we review some sales data together to figure that out?

A. We did.

Tr. 444:12-16 (Schwendeman)

Pacira's 45-L Accelerated (25 °C) Stability Data



Erucic Acid Concentration & pH in Accelerated Sta
of 45 L Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Ac		
						0 mo.	1 mo.	2 mo
1	037188	45L	Skid 300 at Patheon	4/13/2017	25	ND	23	35
2	037189	45L	Skid 300 at Patheon	4/19/2017	25	ND	25	35
3	037190	45L	Skid 300 at Patheon	4/21/2017	25	ND	LT20	33
4	037191	45L	Skid 400 at Patheon	5/9/2017	25	ND	ND	35
5	037192	45L	Skid 400 at Patheon	5/11/2017	25	ND	ND	35
6	037193	45L	Skid 400 at Patheon	5/15/2017	25	ND	ND	35
7	047903	45L	Skid 300 and 400 at Patheon	5/17/2017	25	ND	25	34
8	126837	45L	Skid 300 at Patheon	12/14/2016	25	ND	LT20	35
9	13-2204	45L	Suite C (Skid 200)	7/11/2013	25	ND	ND	22
10	13-2205	45L	Suite C (Skid 200)	7/13/2013	25	ND	LT20	23
11	13-2206	45L	Suite C (Skid 200)	7/15/2013	25	ND	LT20	24
12	14-2107	45L	Suite A	4/26/2014	25	21	38	57
13	14-4001	45L	Suite C (Skid 100)	3/25/2014	25	ND	20	41
14	14-4004	45L	Suite C (Skid 100)	3/31/2014	25	ND	21	42
15	14-4005	45L	Suite C (Skid 100)	4/2/2014	25	LT20	22	40
16	14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36
17	14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36
18	14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36
19	14-P002	45L	Suite C	4/8/2014	25	ND	22	42
20	14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	41
21	15-3138	45L	Suite C (Skid 200)	7/2/2015	25	ND	LT20	35
22	15-3139	45L	Suite C (Skid 200)	7/2/2015	25	ND	LT20	36
23	15-4126	45L	Suite C (Skid 100)	7/2/2015	25	ND	LT20	35
24	16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35
25	16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34
26	16-3090	45L	Suite C (Skid 200)	6/9/2016	25	ND	LT20	36
27	16-P004	45L	Suite C Pooling	6/15/2016	25	ND	LT20	36
28	17-3142	45L	Suite C (Skid 200)	7/4/2017	25	LT20	29	43
29	17-4135	45L	Suite C (Skid 100)	7/3/2017	25	LT20	25	39
30	17-4136	45L	Suite C (Skid 100)	7/4/2017	25	LT20	34	48
31	18-3010	45L	Suite C (Skid 200)	2/10/2018	25	LT20	29	41
32	18-4009	45L	Suite C (Skid 100)	2/9/2018	25	LT20	30	41
33	18-4010	45L	Suite C (Skid 100)	2/10/2018	25	LT20	34	46

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DTX-3110.1

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
1	037188	45L	Skid 300 at Patheon	4/13/2017	25	ND	23	35	46	90	6.7	N	JTX-4049.0037
2	037189	45L	Skid 300 at Patheon	4/19/2017	25	ND	25	35	46	89	6.8	N	JTX-4049.0038
3	037190	45L	Skid 300 at Patheon	4/21/2017	25	ND	LT20	33	45	83	6.8	N	JTX-4049.0039
4	037191	45L	Skid 400 at Patheon	5/9/2017	25	ND	ND	35	44	80	6.9	N	JTX-4049.0040
5	037192	45L	Skid 400 at Patheon	5/11/2017	25	ND	ND	35	43	80	6.9	N	JTX-4049.0041
6	037193	45L	Skid 400 at Patheon	5/15/2017	25	ND	ND	35	42	78	6.9	N	JTX-4049.0042
7	047903	45L	Skid 300 and 400 at Patheon	5/17/2017	25	ND	25	34	43	79	6.8	N	JTX-4049.0043 DTX-2512.20
8	126837	45L	Skid 300 at Patheon	12/14/2016	25	ND	LT20	35	41	102	6.6	N	JTX-4049.0036 DTX-2519.1
9	13-2204	45L	Suite C (Skid 200)	7/11/2013	25	ND	ND	22	36	93	6.7	N	JTX-4049.0020 DTX-2512.17
10	13-2205	45L	Suite C (Skid 200)	7/13/2013	25	ND	LT20	23	35	91	6.7	N	JTX-4049.0021 DTX-2512.17
11	13-2206	45L	Suite C (Skid 200)	7/15/2013	25	ND	LT20	24	37	92	6.7	N	JTX-4049.0022 DTX-2512.17
12	14-2107	45L	Suite A	4/26/2014	25	21	38	57	79	146	6.3	N	JTX-4051.0015
13	14-4001	45L	Suite C (Skid 100)	3/25/2014	25	ND	20	41	58	127	6	N	JTX-4049.0023 DTX-2512.17
14	14-4004	45L	Suite C (Skid 100)	3/31/2014	25	ND	21	42	57	125	6.1	N	JTX-4049.0024 DTX-2512.17
15	14-4005	45L	Suite C (Skid 100)	4/2/2014	25	LT20	22	40	56	122	6.3	N	JTX-4049.0019 DTX-2512.17
16	14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049.0025
17	14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049.0026
18	14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049.0027
19	14-P002	45L	Suite C	4/8/2014	25	ND	22	42	63	135	6.3	N	JTX-4051.0014
20	14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	41	53	118	6.4	Y	JTX-4049.0028
21	15-3138	45L	Suite C (Skid 200)	7/2/2015	25	ND	LT20	35	54	116	6.2	N	JTX-4049.0030
22	15-3139	45L	Suite C (Skid 200)	7/2/2015	25	ND	LT20	36	53	113	6.1	N	JTX-4049.0031
23	15-4126	45L	Suite C (Skid 100)	7/2/2015	25	ND	LT20	35	51	115	6.5	N	JTX-4049.0029
24	16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049.0033
25	16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049.0032 JTX-4079.0002
26	16-3090	45L	Suite C (Skid 200)	6/9/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049.0034
27	16-P004	45L	Suite C Pooling	6/15/2016	25	ND	LT20	36	51	111	6.5	N	JTX-4049.0035
28	17-3142	45L	Suite C (Skid 200)	7/4/2017	25	LT20	29	43	58	114	6.4	N	JTX-4049.0045
29	17-4135	45L	Suite C (Skid 100)	7/3/2017	25	LT20	25	39	54	109	6.5	N	JTX-4049.0044
30	17-4136	45L	Suite C (Skid 100)	7/4/2017	25	LT20	34	48	64	123	6.5	N	JTX-4049.0046
31	18-3010	45L	Suite C (Skid 200)	2/10/2018	25	LT20	29	41	57	107	6.5	N	JTX-4049.0048
32	18-4009	45L	Suite C (Skid 100)	2/9/2018	25	LT20	30	41	58	109	6.6	N	JTX-4049.0047
33	18-4010	45L	Suite C (Skid 100)	2/10/2018	25	LT20	34	46	61	115	6.5	N	JTX-4049.0049

Pacira's 45-L Accelerated (25 °C) Stability Data – Sold Batches

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Commercial Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
1	14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049.0025
2	14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049.0026
3	14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049.0027
4	14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	41	53	118	6.4	Y	JTX-4049.0028
5	16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049.0033
6	16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049.0032 JTX-4079.0002
7	16-3090	45L	Suite C (Skid 200)	6/9/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049.0034
8	18-P003	45L	Suite C (Skid 100 and 200)	6/4/2020	25	LT20	29	42	59	116	6.5	Y	JTX-4049.0051 DTX-2512.23
9	18-P004	45L	Suite C (Skid 100 and 200)	6/5/2020	25	LT20	28	40	56	111	6.5	Y	JTX-4049.0052 DTX-2512.23
10	18-P063	45L	Suite C (Skid 100)	11/29/2020	25	LT20	28	48	62	127	6.5	Y	JTX-4049.0053

Pacira's Interrogatory Response

Moreover, Pacira notes that with respect to the lots included in the reference sample average and % RSD values in Table 1A, those lots were manufactured using the 45 L process. Those lots were chosen because the 25°C stability study data at 1 month, 2 month, 3 month, and 6 month time points for these batches had been collected for a different study called the prefilled syringe stability study, and it was convenient to use the same lots. However, while there were 10

Pharmaceuticals, Inc. and Pacira BioSciences, Inc. (collectively, "Pacira" or "Plaintiffs") hereby provides the following Corrected Second Supplemental Responses and Objections to Defendants eVenus Pharmaceuticals Laboratories Inc. ("eVenus"), Jiangsu Hengrui Pharmaceuticals Co., and

2:21-cv-19829 Defendants' Exhibit DTX-2176

Exhibit # Los 7 06-13-23 KS

DTX-2176.1

DTX-2176.29

Ms. Los: Data Collected for Prefilled Syringe Study Was Used for "Convenience"

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. Ms. Los, was it convenient to use the same lots for the erucic acid stability data in table 1A of the '495 patent and the prefilled syringe study?

A. Yes, it was because the lots that were used for the prefilled syringe study met minimum criteria for a number of data points with measurable erucic acid. And those were the same criteria that we needed to make the comparison for table 1A. And therein lies the convenience, that we had already gone through the exercise of looking to see which lots had enough data to make that comparison.

JTX-4289.36 (Los Tr. 165:3-15)

The Ardekani Data

From: Soroush Ardekani <Soroush.Ardekani@pacira.com>
Sent: Monday, December 7, 2020 7:45 AM
To: Tricia Glenn <Tricia.Glenn@pacira.com>
Cc: Kathy Los <Kathy.Los@pacira.com>; Louie Garcia <Louie.Garcia@pacira.com>; Darrin Christiansen <Darrin.Christiansen@pacira.com>
Subject: EXPAREL stability documentation 5 & 25C

Hi Tricia,

I'm performing an EXPAREL-syringe compatibility study at various temperatures to predict stability changes at 5C. Could you please provide the most recent annual report containing stability tables at 5 & 25C? This will help me identify specific stability indicating attributes to watch out for when starting the study. Please let me know if you have any questions.

Thanks

Soroush

Soroush Ardekani, Ph.D
Scientist II, Pre-clinical R&D
E-mail: soroush.ardekani@pacira.com
Phone: 858-529-3159

PACIRA

DTX-2465.2

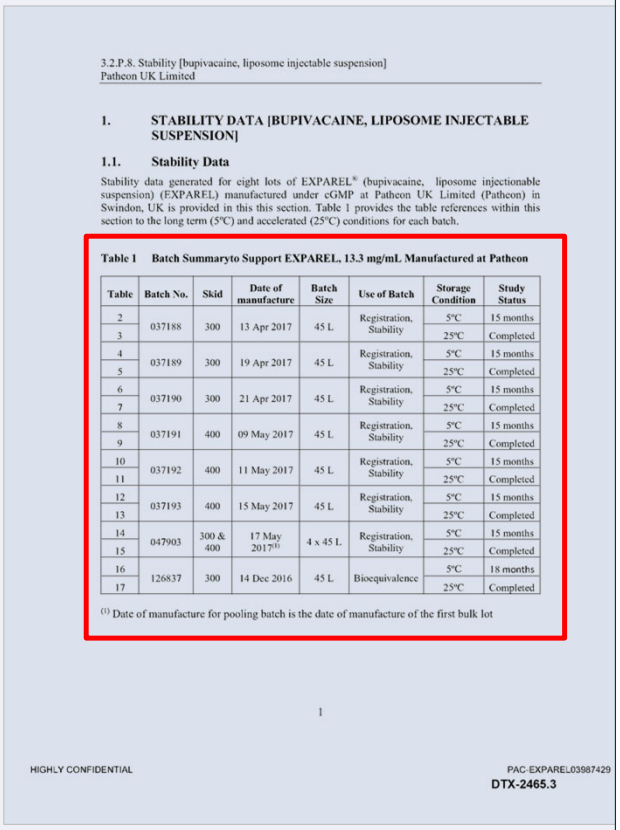
The Ardekani Data

To: Louie Garcia[Louie.Garcia@pacira.com]; Kathy Los[Kathy.Los@pacira.com]
Cc: Paige Davis[Paige.Davis@pacira.com]
From: Soroush Ardekani
Sent: 2020-12-09T18:07:26Z
Importance: Normal
Subject: FW: EXPAREL stability documentation 5 & 25C
Received: 2020-12-09T18:07:37Z
EXPAREL recent stability data.zip

FYI, stability data

DTX-2465.1

The Ardekani Data: Data from Swindon



3.2.P.8. Stability [bupivacaine, liposome injectable suspension]
Patheon UK Limited

1. STABILITY DATA [BUPIVACAINE, LIPOSOME INJECTABLE SUSPENSION]

1.1. Stability Data

Stability data generated for eight lots of EXPAREL® (bupivacaine, liposome injectionable suspension) (EXPAREL) manufactured under cGMP at Patheon UK Limited (Patheon) in Swindon, UK is provided in this section. Table 1 provides the table references within this section to the long term (5°C) and accelerated (25°C) conditions for each batch.

Table 1 Batch Summaryto Support EXPAREL, 13.3 mg/mL Manufactured at Patheon

Table	Batch No.	Skid	Date of manufacture	Batch Size	Use of Batch	Storage Condition	Study Status
2	037188	300	13 Apr 2017	45 L	Registration, Stability	5°C	15 months
3						25°C	Completed
4	037189	300	19 Apr 2017	45 L	Registration, Stability	5°C	15 months
5						25°C	Completed
6	037190	300	21 Apr 2017	45 L	Registration, Stability	5°C	15 months
7						25°C	Completed
8	037191	400	09 May 2017	45 L	Registration, Stability	5°C	15 months
9						25°C	Completed
10	037192	400	11 May 2017	45 L	Registration, Stability	5°C	15 months
11						25°C	Completed
12	037193	400	15 May 2017	45 L	Registration, Stability	5°C	15 months
13						25°C	Completed
14	047903	300 & 400	17 May 2017(1)	4 x 45 L	Registration, Stability	5°C	15 months
15						25°C	Completed
16	126837	300	14 Dec 2016	45 L	Bioequivalence	5°C	18 months
17						25°C	Completed

(1) Date of manufacture for pooling batch is the date of manufacture of the first bulk lot

1

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PAC-EXPAREL03987429
DTX-2465.3

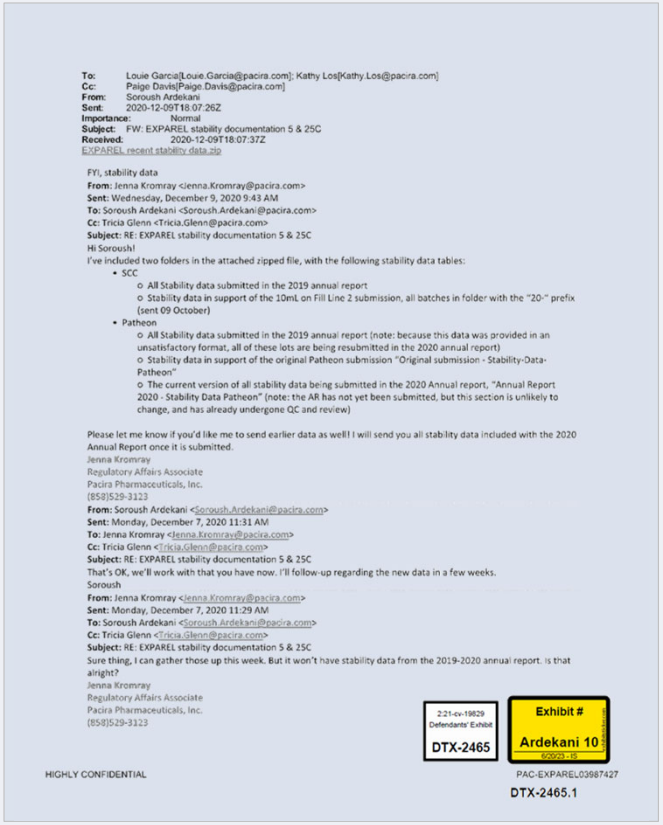
DTX-2465.3

Table 1 Batch Summaryto Support EXPAREL, 13.3 mg/mL Manufactured at Patheon

Table	Batch No.	Skid	Date of manufacture	Batch Size	Use of Batch	Storage Condition	Study Status
2	037188	300	13 Apr 2017	45 L	Registration, Stability	5°C	15 months
3						25°C	Completed
4	037189	300	19 Apr 2017	45 L	Registration, Stability	5°C	15 months
5						25°C	Completed
6	037190	300	21 Apr 2017	45 L	Registration, Stability	5°C	15 months
7						25°C	Completed
8	037191	400	09 May 2017	45 L	Registration, Stability	5°C	15 months
9						25°C	Completed
10	037192	400	11 May 2017	45 L	Registration, Stability	5°C	15 months
11						25°C	Completed
12	037193	400	15 May 2017	45 L	Registration, Stability	5°C	15 months
13						25°C	Completed
14	047903	300 & 400	17 May 2017(1)	4 x 45 L	Registration, Stability	5°C	15 months
15						25°C	Completed
16	126837	300	14 Dec 2016	45 L	Bioequivalence	5°C	18 months
17						25°C	Completed

(1) Date of manufacture for pooling batch is the date of manufacture of the first bulk lot

The Ardekani Data: Data from SCC



To: Louie Garcia[Louie.Garcia@pacira.com]; Kathy Los[Kathy.Los@pacira.com]
Cc: Paige Davis[Paige.Davis@pacira.com]
From: Soroush Ardekani
Sent: 2020-12-09T18:07:26Z
Importance: Normal
Subject: FW: EXPAREL stability documentation 5 & 25C
Received: 2020-12-09T18:07:37Z
EXPAREL recent stability data.zip

FYI, stability data
From: Jenna Kromray <Jenna.Kromray@pacira.com>
Sent: Wednesday, December 9, 2020 9:43 AM
To: Soroush Ardekani <Soroush.Ardekani@pacira.com>
Cc: Tricia Glenn <Tricia.Glenn@pacira.com>
Subject: RE: EXPAREL stability documentation 5 & 25C
Hi Soroush!
I've included two folders in the attached zipped file, with the following stability data tables:

- SCC
  - All Stability data submitted in the 2019 annual report
  - Stability data in support of the 10mL on Fill Line 2 submission, all batches in folder with the "20-" prefix (sent 09 October)
- Patheon
  - All Stability data submitted in the 2019 annual report (note: because this data was provided in an unsatisfactory format, all of these lots are being resubmitted in the 2020 annual report)
  - Stability data in support of the original Patheon submission "Original submission - Stability-Data-Patheon"
  - The current version of all stability data being submitted in the 2020 Annual report, "Annual Report 2020 - Stability Data Patheon" (note: the AR has not yet been submitted, but this section is unlikely to change, and has already undergone QC and review)

Please let me know if you'd like me to send earlier data as well! I will send you all stability data included with the 2020 Annual Report once it is submitted.
Jenna Kromray
Regulatory Affairs Associate
Pacira Pharmaceuticals, Inc.
(858)529-3123
From: Soroush Ardekani <Soroush.Ardekani@pacira.com>
Sent: Monday, December 7, 2020 11:31 AM
To: Jenna Kromray <Jenna.Kromray@pacira.com>
Cc: Tricia Glenn <Tricia.Glenn@pacira.com>
Subject: RE: EXPAREL stability documentation 5 & 25C
That's OK, we'll work with that you have now. I'll follow-up regarding the new data in a few weeks.
Soroush
From: Jenna Kromray <Jenna.Kromray@pacira.com>
Sent: Monday, December 7, 2020 11:29 AM
To: Soroush Ardekani <Soroush.Ardekani@pacira.com>
Cc: Tricia Glenn <Tricia.Glenn@pacira.com>
Subject: RE: EXPAREL stability documentation 5 & 25C
Sure thing, I can gather those up this week. But it won't have stability data from the 2019-2020 annual report. Is that alright?
Jenna Kromray
Regulatory Affairs Associate
Pacira Pharmaceuticals, Inc.
(858)529-3123

2:21-cv-19829 Defendants' Exhibit DTX-2465

Exhibit # Ardekani 10

HIGHLY CONFIDENTIAL

PAC-EXPAREL03987427
DTX-2465.1

DTX-2465.20

3.2.P.3. Manufacture [bupivacaine, liposome injectable suspension]

1. MANUFACTURERS [BUPIVACAINE, LIPOSOME INJECTABLE SUSPENSION]

EXPAREL® is manufactured by Pacira Pharmaceuticals Inc. in San Diego, CA. Pacira's manufacturing campus is comprised of two buildings, designated as Building 1 and Building 7 (GMP warehouse). Both buildings are located within five miles of each other, on separate and distinct sites.

The manufacture of EXPAREL and its initial product release and stability testing are conducted in accordance with current Good Manufacturing Practices (US, EU) in Pacira's Building 1.

Building 1 is a 79,000 square foot concrete tilt-up structure located on a 4.98 acre site. It was custom-built as a pharmaceutical R&D and manufacturing facility in August of 1995. Activities in this facility include the manufacture of the bulk EXPAREL product and its fill/finish into vials, microbiological and quality control testing, product storage, development of analytical methods, research and development, the coordination of clinical and regulatory functions, and the location of general administrative functions. Approximately 14,000 square feet are used for manufacturing. Bulk manufacturing areas are generally Grade C / Class 10,000, with Grade D / Class 100,000 support rooms, and are supplied with various clean utility systems, such as water for injection (WFI), clean steam, clean compressed air, and nitrogen. EXPAREL is filled in a Grade A / Class 100 area, surrounded by a Grade B / Class 1,000 area, both of which are supplied with nitrogen and clean compressed air systems. Specific details of the room environments are provided in Section 3.2.A.1.9, Aseptic Validation Package, Room Classifications.

Building 7 (GMP warehouse) is an approximately 20,000 square foot concrete tilt-up structure located within five miles of the B1 manufacturing facility. The B7 facility is a GMP warehouse used to receive, sample and distribute raw materials to the bulk manufacturing facilities located at Building 1 (EXPAREL). Building 7 is also used to store analytical retain samples of drug substance, excipients, components and drug product. Qualification of the B7 as a GMP warehouse is described in Section 3.2.P.3.5, Process Validation and/or Evaluation (Building 7).

Both locations are covered under the same Quality Management System which is administered by Quality Assurance located in the B1 facility.

Activities performed by Pacira, as well contract manufacturing organizations and laboratories used for various analytical procedures are listed in Table 1.

Ms. Los: Prepared The Los Spreadsheet

Kathleen Los

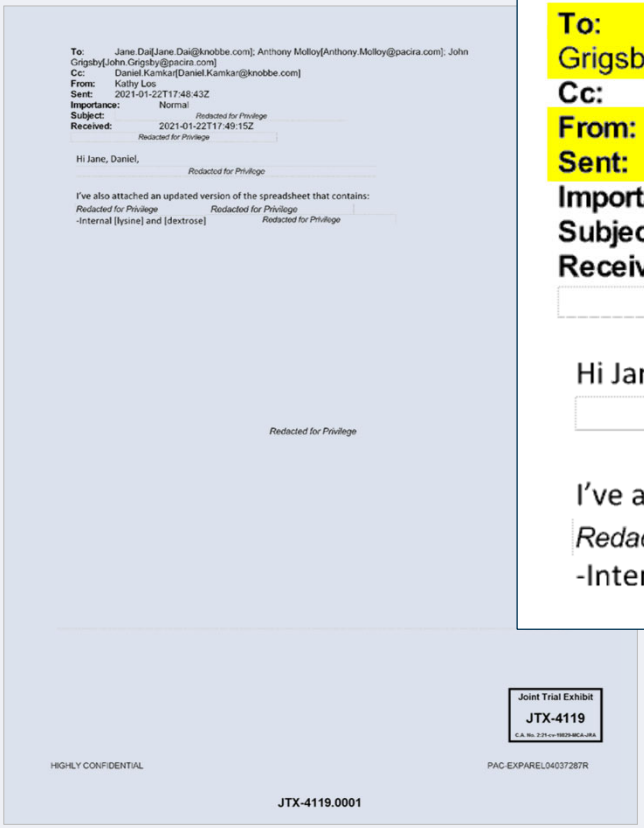
PACIRA PHARMACEUTICALS, INC.

Q. You prepared a spreadsheet, an Excel spreadsheet, that served as the basis of the data in the asserted patents; correct?

A. That's correct.

JTX-4289.18 (Los Tr. 91:13-16)

The Los Spreadsheet



To: Jane.Dai[Jane.Dai@knobbe.com]; Anthony Molloy[Anthony.Molloy@pacira.com]; John Grigsby[John.Grigsby@pacira.com]
Cc: Daniel.Kamkar[Daniel.Kamkar@knobbe.com]
From: Kathy Los
Sent: 2021-01-22T17:48:43Z
Importance: Normal
Subject: *Redacted for Privilege*
Received: 2021-01-22T17:49:15Z
Redacted for Privilege

Hi Jane, Daniel,

Redacted for Privilege

I've also attached an updated version of the spreadsheet that contains:

Redacted for Privilege *Redacted for Privilege*
-Internal [lysine] and [dextrose] *Redacted for Privilege*

JTX-4119.1

The Los Spreadsheet

Redacted for Privilege

			Erucic Acid (ug/ml) NMT 310			
200L Swindon	Lot	0	1m	2m	3m	6m
	129855	ND	22	36	54	99
	129856	ND	23	38	51	99
	129860	ND	23	38	54	98
Average			22.7	37.3	53.0	98.7
% RSD			2.5	3.1	3.3	0.6

Redacted for Privilege

Redacted for Privilege

45L SCC	Lot	0	1m	2m	3m	6m
	20-3066	ND	28	35	52	NA
	20-3067	28	41	57	75	NA
	20-4076	27	43	59	70	NA
	16-p004-pool	ND	LT 20	36	51	111
	16-3088-200	ND	25	35	53	110
	16-3089-200	ND	LT 20	34	54	111
	16-3090-200	ND	LT 20	36	54	114
	17-3142	LT 20	29	43	58	114
	17-4135	LT 20	25	39	54	109
	17-4136	LT 20	34	48	64	123
Average			28.3	38.7	55.4	113.1
% RSD			26.2	24.3	15.0	4.2

Redacted for Privilege

Redacted for Privilege

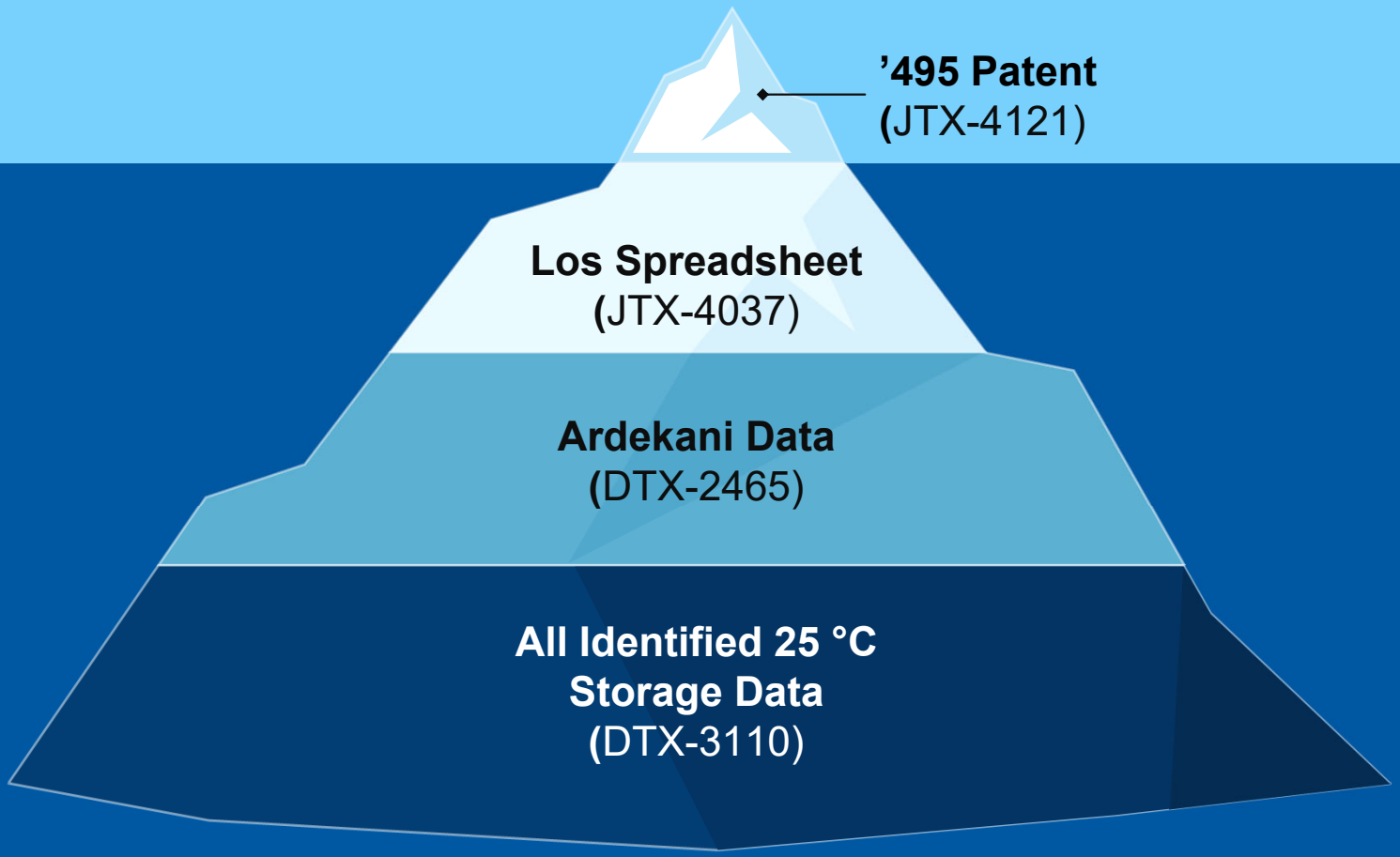
JTX-4037.18

		Erucic Acid (ug/ml) NMT 310				
200L Swindon	Lot	0	1m	2m	3m	6m
	129855	ND	22	36	54	99
	129856	ND	23	38	51	99
	129860	ND	23	38	54	98
Average			22.7	37.3	53.0	98.7
% RSD			2.5	3.1	3.3	0.6

45L SCC	Lot	0	1m	2m	3m	6m
	20-3066	ND	28	35	52	NA
	20-3067	28	41	57	75	NA
	20-4076	27	43	59	70	NA
	16-p004-pool	ND	LT 20	36	51	111
	16-3088-200	ND	25	35	53	110
	16-3089-200	ND	LT 20	34	54	111
	16-3090-200	ND	LT 20	36	54	114
	17-3142	LT 20	29	43	58	114
	17-4135	LT 20	25	39	54	109
	17-4136	LT 20	34	48	64	123
Average			28.3	38.7	55.4	113.1
% RSD			26.2	24.3	15.0	4.2

JTX-4037.18

Pacira's 45-L Data



Inequitable Conduct

Inequitable Conduct

"To prove inequitable conduct, the challenger must show by clear and convincing evidence that the patent applicant (1) misrepresented or omitted information material to patentability, and (2) did so with specific intent to mislead or deceive the PTO."

Ohio Willow Wood Co. v. Alps S., 735 F.3d 1333, 1344 (Fed. Cir. 2013)
(internal citations and quotations omitted)

Inequitable Conduct

"To satisfy the intent requirement, the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it."

Belcher Pharms., LLC v. Hospira, 11 F.4th 1345, 1353 (Fed. Cir. 2021) (internal citations and quotations omitted)

"In particular, undisclosed prior art is 'but-for material if the PTO would not have allowed a claim had it been aware of' it."

Am. Calcar, Inc. v. Am. Honda Motor Co., 768 F.3d 1185, 1189 (Fed. Cir. 2014)
(quoting *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1291 (Fed. Cir. 2011)

"When the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material."

Therasense, 649 F.3d at 1292

Inequitable Conduct

"'[B]ecause direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence,' provided that such intent is the single reasonable inference."

Am. Calcar, 768 F.3d at 1190–91
(quoting *Therasense,* 649 F.3d at 1290-91)

Inequitable Conduct: Materiality

Inequitable Conduct – Materiality During Prosecution vs. But-for Materiality

litigation statements, and the like. "Materiality is not limited to prior art but embraces *any* information that a reasonable examiner would be substantially likely to consider important in deciding whether to allow an application to issue as a patent." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234, 66 USPQ2d 1481, 1486 (Fed. Cir. 2003) (emphasis in original) (finding article which was not prior art to be material to enablement issue).

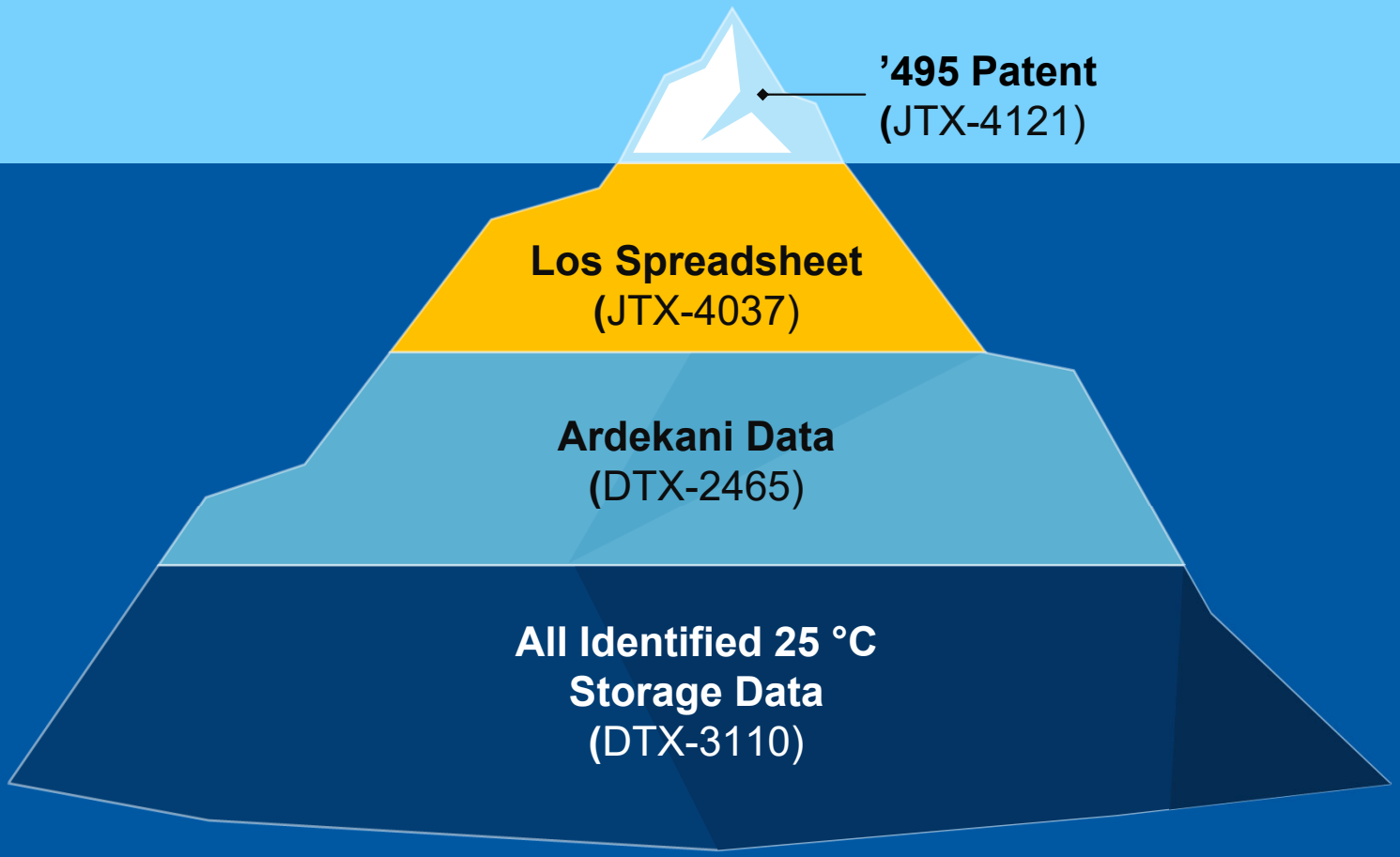
During Prosecution: Definition of "Materiality" for Compliance with Duty of Candor (MPEP § 2001)

This court holds that, as a general matter, the materiality required to establish inequitable conduct is but-for materiality. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art. Hence, in assessing the materiality of

During Litigation: Definition of "But-for Materiality" For Inequitable Conduct (*Therasense*)

MPEP § 2001 (June 2020) (DTX-2200.4); *Therasense*, 649 F.3d at 1291.

Pacira's 45-L Data



Erucic Acid Stability Data in the '495 Patent

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

JTX-4121.19, Table 1A at 20:47-67

45L SCC	Lot	0	1m	2m	3m	6m
	20-3066	ND	28	35	52	NA
	20-3067	28	41	57	75	NA
	20-4076	27	43	59	70	NA
	16-p004-pool	ND	LT 20	36	51	111
	16-3088-200	ND	25	35	53	110
	16-3089-200	ND	LT 20	34	54	111
	16-3090-200	ND	LT 20	36	54	114
	17-3142	LT 20	29	43	58	114
	17-4135	LT 20	25	39	54	109
	17-4136	LT 20	34	48	64	123
Average			28.3	38.7	55.4	113.1
% RSD			26.2	24.3	15.0	4.2

JTX-4037.18

Dr. Dai: Drafted Table 1A

Dr. Jane Dai

Q. Stability data on the erucic acid concentration as a function of time is presented in table 1A of the '495 patent; correct?

A. Yes, erucic acid – table says erucic acid concentration as a function of time.

Q. Who drafted table 1A in the '495 patent?

A. I worked with my associate Daniel Kamkar.

JTX-4288.8 (Dai Tr. 94:14-20)

Dr. Dai: Chose to Exclude Data in Los Spreadsheet from Table 1A

Dr. Jane Dai

Q. Did you review this spreadsheet in connection with prosecution of the asserted patents?

A. Yes.

Q. Is the data in this spreadsheet the basis for the data tables in the asserted patents?

A. Yes.

* * *

Q. The bottom half of this page has a section "45L SCC"; right?

A. Yes.

Q. This section provides erucic acid stability data on ten lots of 45-liter Exparel; right?

A. Yes.

Q. Is this 45-liter data the data underlying the reference samples reported in table 1A of the asserted patents?

A. Yes.

***

Q. Was any of the data, on individual batches of 45-liter Exparel in Exhibit 7, provided to the patent office, during prosecution of the asserted patents?

A. No, not the individual batch.

JTX-4288.10-12
(Dai Tr. 114:20-21, 114:25-115:3, 118:12-21, 127:09-12, 127:15)

Ms. Los: Possible to Report Individual Data Points

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. It would be possible to report individual batch values in the patent rather than an average; correct?

A. It would be possible.

JTX-4289.26 (Los Tr. 129:17-19, 129:23)

Table 1A Could Have Included Individual Batch Data

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
1	**LT 20**	**36**	**51**	**111**
2	**25**	**35**	**53**	**110**
3	**LT 20**	**34**	**54**	**111**
4	**LT 20**	**36**	**54**	**114**
5	**29**	**43**	**58**	**114**
6	**25**	**39**	**54**	**109**
7	**34**	**48**	**64**	**123**
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

Table 1A Could Have Included Individual Batch Data

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
1	**LT 20**	**36**	**51**	**111**
2	**25**	**35**	**53**	**110**
3	**LT 20**	**34**	**54**	**111**
4	**LT 20**	**36**	**54**	**114**
5	**29**	**43**	**58**	**114**
6	**25**	**39**	**54**	**109**
7	**34**	**48**	**64**	**123**
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

Inequitable Conduct – "n/a" in Table 1A

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

JTX-4121.19, Table 1A at 20:47-67

Dr. Dai: Chose to Use "n/a"

Dr. Jane Dai

Q. Who drafted this N/A in the one-month column for the average of the reference samples in table 1A?

A. It would be either myself or associate Mr. Daniel Kamkar.

JTX-4288.9 (Dai Tr. 98:1-3, 98:6-7)

Ms. Los: Excuse for "n/a"

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. If you wanted to calculate the true average one-month value, you would need to come up with some way to take into account these less than values; right?

A. The true average can only be calculated from those lots that have data for them.

Q. So your stance, Ms. Los, is that by removing all of the low values, you can accurately calculate the average?

A. No, I'm not saying that – I don't know. There's no good way of handling the data when you don't have reportable numbers for some of your data points. I mean, you have – you have to settle on what is the best way without inventing data and that's what we did.

JTX-4289.25-26 (Los Tr. 128:22-25, 129:3-7, 129:11-16)

Dr. Schwendeman: "n/a" Needs Explanation

Dr. Anna Schwendeman

Q. Well, if it means not applicable, wouldn't it be right because you can't calculate an average since some of the batches had less than 20 and not a number, how could you report that data?

A. When I put my tables or my students put their tables because N/A is not available or not applicable, I always require to put estimates and describe what N/A refers to.

Q. Is there another way you could report the data accurately for the reference samples even if you have some less than 20s or nondetecteds?

A. Yes, you can put all the individual data points and this would allow for a person to see what the range was.

Tr. 426:24-427:10 (Schwendeman)

Table 1A Could Have Included an Explanation for "n/a"

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

n/a: At the 1 month time point, several batches of the reference samples contained erucic acid at concentrations below the lower limit of detection of the assay (20 µg/mL). Therefore, an average value of erucic acid concentration for all batches of the reference samples could not be calculated at the 1 month time point.

Ms. Los: Used "n/a" to Mean "Not Available"

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. We saw earlier that, in your internal spreadsheet, "n/a" means no data available; right?

A. Yes, in my – the spreadsheet I've created or consolidated, a combination of the two, I used "n/a" to mean not available, as those data were not yet available.

***

Q. So one reasonable reading of the "n/a" in table 1A of the '495 patent is that data was not available for one month for the reference samples?

A. That's right. I –

A. I agree that's a possible reading of that.

JTX-4289.39-40 (Los Tr. 171:3-4, 171:7-10, 172:22-25, 173:2)

Dr. Dai: Inconsistent Testimony on "n/a"

Dr. Jane Dai

Q. Outside the context of this patent, Dr. Dai, are you familiar with the abbreviation N/A?

A. Yes.

Q. What does N/A typically mean?

A. It means not applicable.

***

Q. If you look at the top three batches, the six-month value reported is N/A. Do you see that?

A. Yes.

Q. What does that N/A mean?

A. It means not available.

JTX-4288.9, 11-12 (Dai Tr. 98:8-12, 119:25-120:5)

Dr. Ardekani: "n/a" Means There Is No Data Available

Dr. Soroush Ardekani

PACIRA PHARMACEUTICALS, INC.

Q. Do you have an understanding as to why Table 1A says "N/A" for the one month data for the 45-liter batches, even though you had that data?

A. I don't know.

Q. Would you ever use an "N/A" to indicate that there was data?

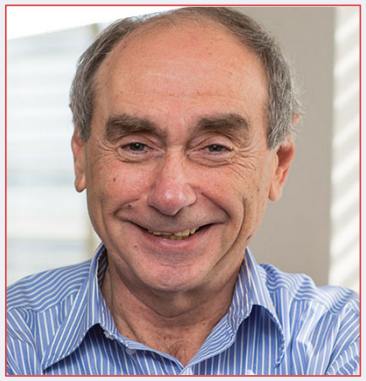
A. I wouldn't, no.

Q. I'm asking you, Dr. Ardekani, your personal understanding as a scientist, when you see "N/A" in a data table, is your assumption that the data exists but the person has chosen not to provide it?

A. No, that's not my assumption. My assumption is that it doesn't – it's not there.

JTX-4287.11 (Ardekani Tr. 115:22-24, 116:4, 116:22-23, 116:25, 117:15-19, 117:22-23

Dr. Klibanov: Excuse for Averaging



Dr. Alexander Klibanov

Q. Now, do you agree with Dr. Schwendeman that there is no scientific basis to report the values for 45-liter reference batches as averages?

A. No, I do not. I know that the term "averages" was much maligned last week, but the fact of the matter is that averages are often used in scientific literature when the number of individual data points is substantial. For example, usually exceeds 3 to 5. And here it is 7.

Tr. 754:12-19 (Klibanov)

’495 Patent, Table 2B

TABLE 2B

External and internal pH in bupivacaine MVL compositions

Batch	Internal pH	Avg Internal pH	Time 0 Sup pH
1	5.49	5.50	7.4
2	5.51		
3	5.50		
	Ref. samples	5.38	7.1

JTX-4121.20, Table 2B at 22:17-27

Los Spreadsheet – Underlying Data for Table 2B

Y	Z	AA	AB	AC	AD
Skid	Lot	Msmt #1	Msmt #2	Avg	Av of lots
200L Swindon	129855	5.49	5.48	5.49	5.50
	129856	5.51	5.51	5.51	
	129860	5.50	5.49	5.50	
45L SCC	19-3079	5.43	5.42	5.43	5.38
	19-3091	5.34	5.34	5.34	

JTX-4037.28

Inequitable Conduct – Fig. 3B and Table 1A

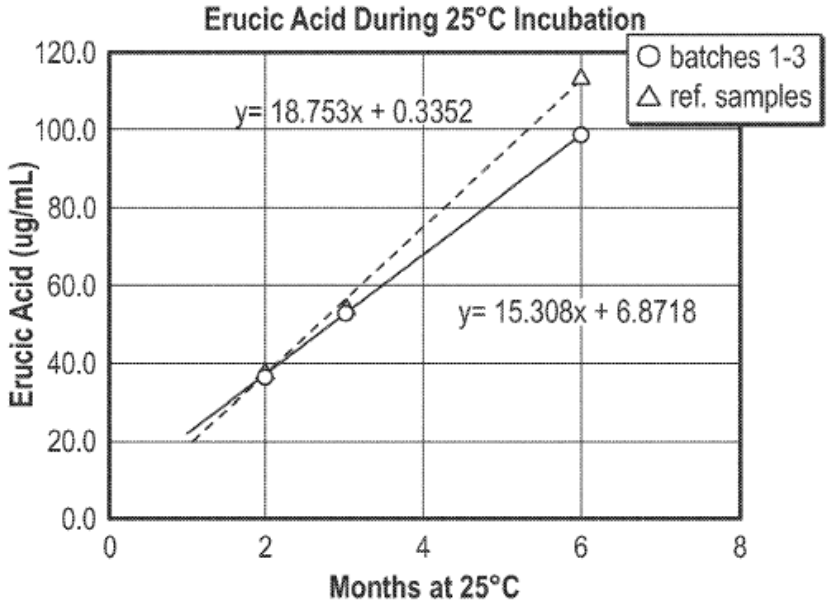


FIG. 3B

JTX-4121.8, Fig. 3B

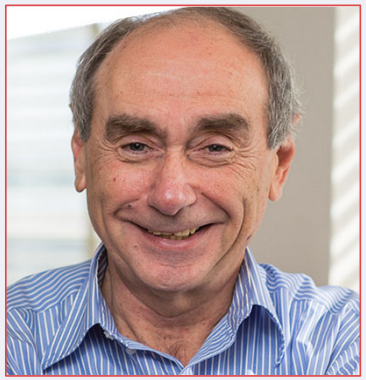
TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

JTX-4121.19, Table 1A at 20:47-67

Dr. Klibanov: POSA Could Not Use Figure 3B to Determine Whether Individual Batches Met Limitations



Dr. Alexander Klibanov

Q. Right. And you agree that a person of ordinary skill in the art could not, looking at Figure 3B, glean whether any individual batch met those two limitations, right?

A. Not with respect to a particular individual batch. With respect to averages, one could.

Q. But you understand the claims are directed to compositions, not averages, right?

A. It's directed to a composition.

Q. And you understand an individual batch would be a composition, right?

A. An individual batch will be a composition.

Tr. 777:19-778:4 (Klibanov)

Inequitable Conduct – Fig. 3B and Table 1A

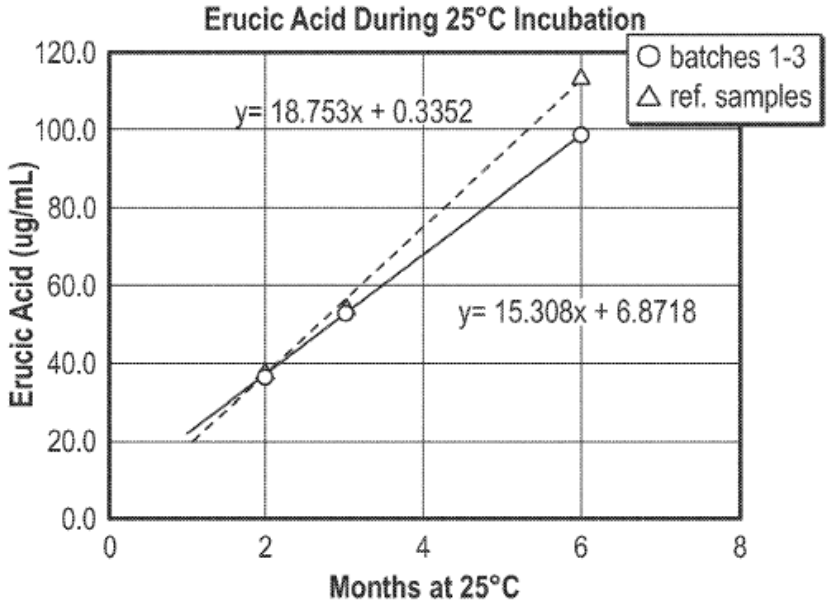


FIG. 3B

JTX-4121.8, Fig. 3B

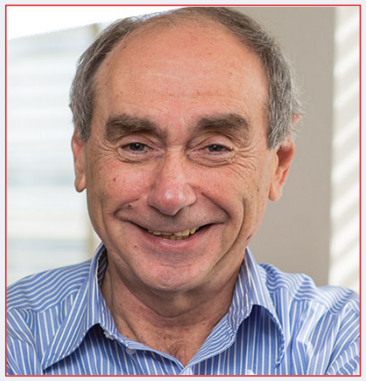
TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

JTX-4121.19, Table 1A at 20:47-67

Dr. Klibanov: "Extrapolation" In Fig. 3B Is Inaccurate



Dr. Alexander Klibanov

Q. Can we go back to Table 1A. It reports 22.7 as the average for one month for the three batches, correct?

A. Yes.

* * *

Q. And if we plug 1 in for X, we should get the result for the one-month results, correct?

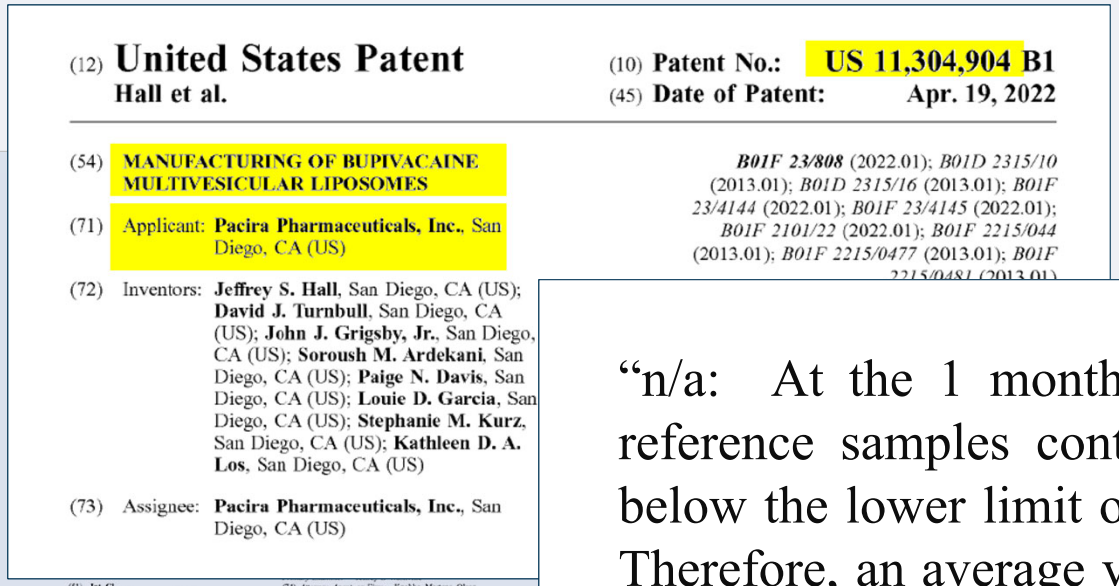
A. Yes, based on the extrapolation.

Q. Right. And if we plug 1 into that equation, we don't get 22.7, do we, sir?

A. We get – just a second, let me just do the math in my head. We get a similar number but not exactly the same number.

Tr. 775:5-8, 14-22 (Klibanov)

Inequitable Conduct – Table 1A Clarified In Later Patents



(12) **United States Patent**
Hall et al.

(10) **Patent No.: US 11,304,904 B1**
(45) **Date of Patent: Apr. 19, 2022**

(54) **MANUFACTURING OF BUPIVACAINE MULTIVESICULAR LIPOSOMES**

(71) Applicant: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(72) Inventors: **Jeffrey S. Hall**, San Diego, CA (US); **David J. Turnbull**, San Diego, CA (US); **John J. Grigsby, Jr.**, San Diego, CA (US); **Soroush M. Ardekani**, San Diego, CA (US); **Paige N. Davis**, San Diego, CA (US); **Louie D. Garcia**, San Diego, CA (US); **Stephanie M. Kurz**, San Diego, CA (US); **Kathleen D. A. Los**, San Diego, CA (US)

(73) Assignee: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

B01F 23/808 (2022.01); *B01D 2315/10* (2013.01); *B01D 2315/16* (2013.01); *B01F 23/4144* (2022.01); *B01F 23/4145* (2022.01); *B01F 2101/22* (2022.01); *B01F 2215/044* (2013.01); *B01F 2215/0477* (2013.01); *B01F*

(74) *Attorney, Agent, or Firm* — Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

Embodiments of the present application relate to commercial manufacturing processes for making bupivacaine multivesicular liposomes (MVLs) using independently operating dual tangential flow filtration modules.

35 Claims, 5 Drawing Sheets

Joint Trial Exhibit
JTX-4131

PAC-EXPAREL01044954

JTX-4131.0001

"n/a: At the 1 month time point, several batches of the reference samples contained erucic acid at concentrations below the lower limit of detection of the assay (20 µg/mL). Therefore, an average value of erucic acid concentration for all batches of the reference samples could not be calculated at the 1 month time point."

See, e.g., JTX-4131.20-21 at 20:65-21:3

Mr. Godici: Footnote In Later Patents Contains New Information

Nicholas Godici

Q. Do you see the language in this footnote?

A. I see it, yes.

Q. That refers to the lower limit of detention of the assay, in parenthesis, 20 micrograms per milliliter?

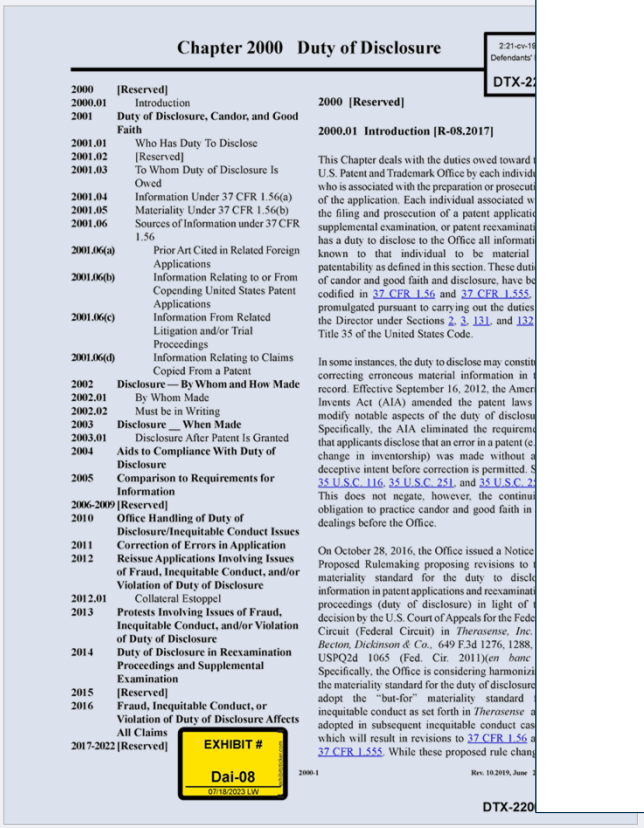
A. I see that. Okay. Yes.

Q. The lower limit of detection of this assay doesn't appear in the previous version of the specification, right?

A. My understanding is no, that it's not, but my point being the examiner reviewed this footnote for content of whether or not it introduced new matter, and my point is that the examiner did not object to this and indicated that based on the understanding that he had, this entire footnote was supported by the original disclosure.

Tr. 855:12-24 (Godici)

MPEP Chapter 2000 – Best Practice Is to Document Basis for Withholding Information



Chapter 2000 Duty of Disclosure

2:21-cv-19 Defendants'

DTX-22

2000 [Reserved]
2000.01 Introduction
2001 Duty of Disclosure, Candor, and Good Faith
2001.01 Who Has Duty To Disclose
2001.02 [Reserved]
2001.03 To Whom Duty of Disclosure Is Owed
2001.04 Information Under 37 CFR 1.56(a)
2001.05 Materiality Under 37 CFR 1.56(b)
2001.06 Sources of Information under 37 CFR 1.56
2001.06(a) Prior Art Cited in Related Foreign Applications
2001.06(b) Information Relating to or From Copending United States Patent Applications
2001.06(c) Information From Related Litigation and/or Trial Proceedings
2001.06(d) Information Relating to Claims Copied From a Patent
2002 Disclosure — By Whom and How Made
2002.01 By Whom Made
2002.02 Must be in Writing
2003 Disclosure — When Made
2003.01 Disclosure After Patent Is Granted
2004 Aids to Compliance With Duty of Disclosure
2005 Comparison to Requirements for Information
2006-2009 [Reserved]
2010 Office Handling of Duty of Disclosure/Inequitable Conduct Issues
2011 Correction of Errors in Application
2012 Reissue Applications Involving Issues of Fraud, Inequitable Conduct, and/or Violation of Duty of Disclosure
2012.01 Collateral Estoppel
2013 Protests Involving Issues of Fraud, Inequitable Conduct, and/or Violation of Duty of Disclosure
2014 Duty of Disclosure in Reexamination Proceedings and Supplemental Examination
2015 [Reserved]
2016 Fraud, Inequitable Conduct, or Violation of Duty of Disclosure Affects All Claims
2017-2022 [Reserved]

EXHIBIT # Dai-08 07/18/2023 LW

2000 [Reserved]

2000.01 Introduction [R-08.2017]

This Chapter deals with the duties owed toward t U.S. Patent and Trademark Office by each individu who is associated with the preparation or prosecuti of the application. Each individual associated w the filing and prosecution of a patent applicatio supplemental examination, or patent reexaminati has a duty to disclose to the Office all informati known to that individual to be material patentability as defined in this section. These duti of candor and good faith and disclosure, have be codified in 37 CFR 1.56 and 37 CFR 1.555, promulgated pursuant to carrying out the duties the Director under Sections 2, 3, 131, and 132 Title 35 of the United States Code.

In some instances, the duty to disclose may consti correcting erroneous material information in t record. Effective September 16, 2012, the Amer Invents Act (AIA) amended the patent laws modify notable aspects of the duty of disclosu Specifically, the AIA eliminated the requirem that applicants disclose that an error in a patent (e change in inventorship) was made without deceptive intent before correction is permitted. S 35 U.S.C. 116, 35 U.S.C. 251, and 35 U.S.C. 2 This does not negate, however, the continui obligation to practice candor and good faith in dealings before the Office.

On October 28, 2016, the Office issued a Notice Proposed Rulemaking proposing revisions to t materiality standard for the duty to disclo information in patent applications and reexaminati proceedings (duty of disclosure) in light of t decision by the U.S. Court of Appeals for the Fede Circuit (Federal Circuit) in *Therasense, Inc. Becton, Dickinson & Co.*, 649 F.3d 1276, 1288, USPQ2d 1065 (Fed. Cir. 2011)(*en banc* Specifically, the Office is considering harmonizi the materiality standard for the duty of disclosure adopt the "but-for" materiality standard inequitable conduct as set forth in *Therasense* a adopted in subsequent inequitable conduct cas which will result in revisions to 37 CFR 1.56 a 37 CFR 1.555. While these proposed rule chang

2000-1 Rev. 10.2019, June

DTX-220

18. Finally, if information was specifically considered and discarded as not material, this fact might be recorded in an attorney's file or applicant's file, including the reason for discarding it. If judgment might have been bad or something might have been overlooked inadvertently, a note made at the time of evaluation might be an invaluable aid in explaining that the mistake was honest and excusable. Though such records are not required, they could be helpful in recalling and explaining actions in the event of a question of "fraud" or "inequitable conduct" raised at a later time.

DTX-2200.13

Dr. Dai: Failed to Document Basis for Withholding Data

Dr. Jane Dai

Q. During prosecution of the asserted patents, did you make any such note with respect to the 45-liter batch data in Exhibit 7 [the Los Spreadsheet]?

A. No, I did not make any note.

JTX-4288.16 (Dai Tr. 137:12-14, 138:2)

Mr. Godici: Attempts to Reinterpret Claim 1

Nicholas Godici

Q. So in your view, Mr. Godici, Claim 1, which recites a limitation only to one-month erucic acid concentration, was allowed because of differences at the six months timepoint?

A. Well, it – I might agree, but really, it's the patent office that says that. It's clearly in the record. The examiner says it here. So that's the position of the patent office with respect to why the claims were allowed.

Tr. 842:14-20 (Godici)

Dr. Dai: Scope of Claim 1 Limited to One-Month Data

Dr. Jane Dai

Q. Claims 1 of each of the asserted patents had a limitation relating to one-month stability data, not six-month stability data; correct?

A. Yeah, Claim 1 recites, [As read] Wherein erucic acid concentration in the composition is about 23 micrograms per milliliter or less after the composition is stored at 25 degrees for one month.

JTX-4288.7 (Dai Tr. 89:24-90:1, 90:11-14)

Ms. Los: Scope of Claim 1 Limited to One-Month Data

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. Claim 1 of the '495 patent only relates to one-month data; correct?

A. Yes.

JTX-4289.49 (Los Tr. 218:18-20)

Dr. Ardekani: Scope of Claim 1 Limited to One-Month Data

Dr. Soroush Ardekani

PACIRA PHARMACEUTICALS, INC.

Q. Carrying on to the very bottom of claim 1 on the next page in column 23, do you see that the last clause of claim one says: "Wherein the erucic acid concentration in the composition is about 23 micrograms per milliliter or less after the composition is stored at 25 degrees celsius for one month"?

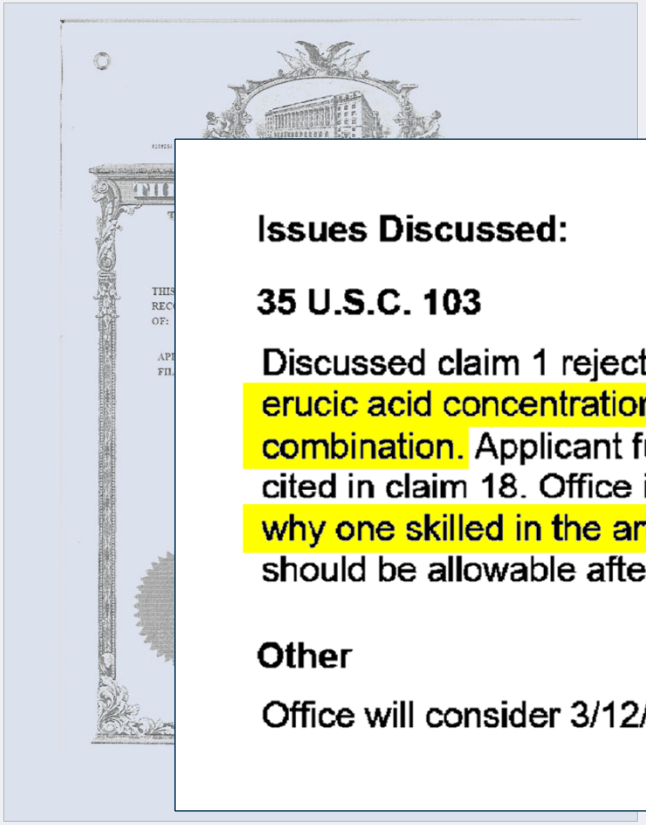
A. Okay.

Q. Sitting here today, can you identify any physical property of the product other than the erucic acid concentration that is new in claim 1 for the 200-liter product?

A. No.

JTX-4287.6-7 (Ardekani Tr. 78:12-19, 80:13-16, 80:18)

’495 Patent File History – Interview Focused on One-Month Data



Issues Discussed:

35 U.S.C. 103

Discussed claim 1 rejection and Applicants argued that the combination does not teach the amount of erucic acid concentration after one month as the product by process is more stable than the cited art combination. Applicant further argues that the process allows higher concentrations of bupivacaine as cited in claim 18. Office indicated that adding claims 17 and 18 to claim 1 and providing a declaration of why one skilled in the art would not expect the prior art to have the same claimed acid concentration should be allowable after a final search and consideration of the 3/12/2021 ids.

Other

Office will consider 3/12/2021 ids in next action

’495 Patent File History (JTX-4001.2167)

"Broadest Reasonable Interpretation"

"In making this patentability determination [i.e., assessing but-for materiality], the court should apply the preponderance of the evidence standard and give claims their broadest reasonable construction."

Therasense, Inc. v. Becton, Dickinson & Co., 649 F.3d 1276, 1291-92 (Fed. Cir. 2011) (en banc)

"Unlike the clear and convincing evidence standard for invalidating a patent in the district court under 35 U.S.C. §§ 102 and 103, the standard for establishing but-for materiality in the inequitable conduct context only requires a preponderance of the evidence, giving claims their broadest reasonable construction."

Aventis Pharma S.A. v. Hospira, Inc., 675 F.3d 1324, 1334 (Fed. Cir. 2012) (quote and citation omitted)

Mr. Molloy: Claim 1 Does Not Discuss Rate of Hydrolysis

Anthony Molloy

PACIRA PHARMACEUTICALS, INC.

Q. Claim 1 [of the '495 patent] doesn't talk about the rate of hydrolysis, right?

A. So the text of Claim 1 does not talk about that. However, I think these claims, you're reading them in isolation. There was a Markman order. There's a specification. So – so Claim 1, you're correct, does not use the phrase "rate of hydrolysis."

Tr. 353:22-354:2 (Molloy)

Mr. Molloy: Different Patent Claims Rate of Hydrolysis

Anthony Molloy

PACIRA PHARMACEUTICALS, INC.

Q. It's [U.S. Patent 11,452,691 is] another one of the Pacira patents in the same family related to the 200-liter process, correct?

A. Yes.

***

Q. So this claim [claim 1 of the '691 patent] does actually talk about the rate of hydrolysis, correct?

A. This claim does.

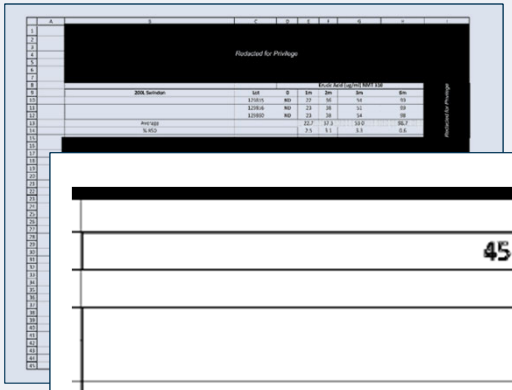
***

Q. And Pacira gave a covenant not to sue to the defendants for this patent, right?

A. Oh, we did, yes.

Tr. 354:6-8, 354:23-25, 355:9-11 (Molloy)

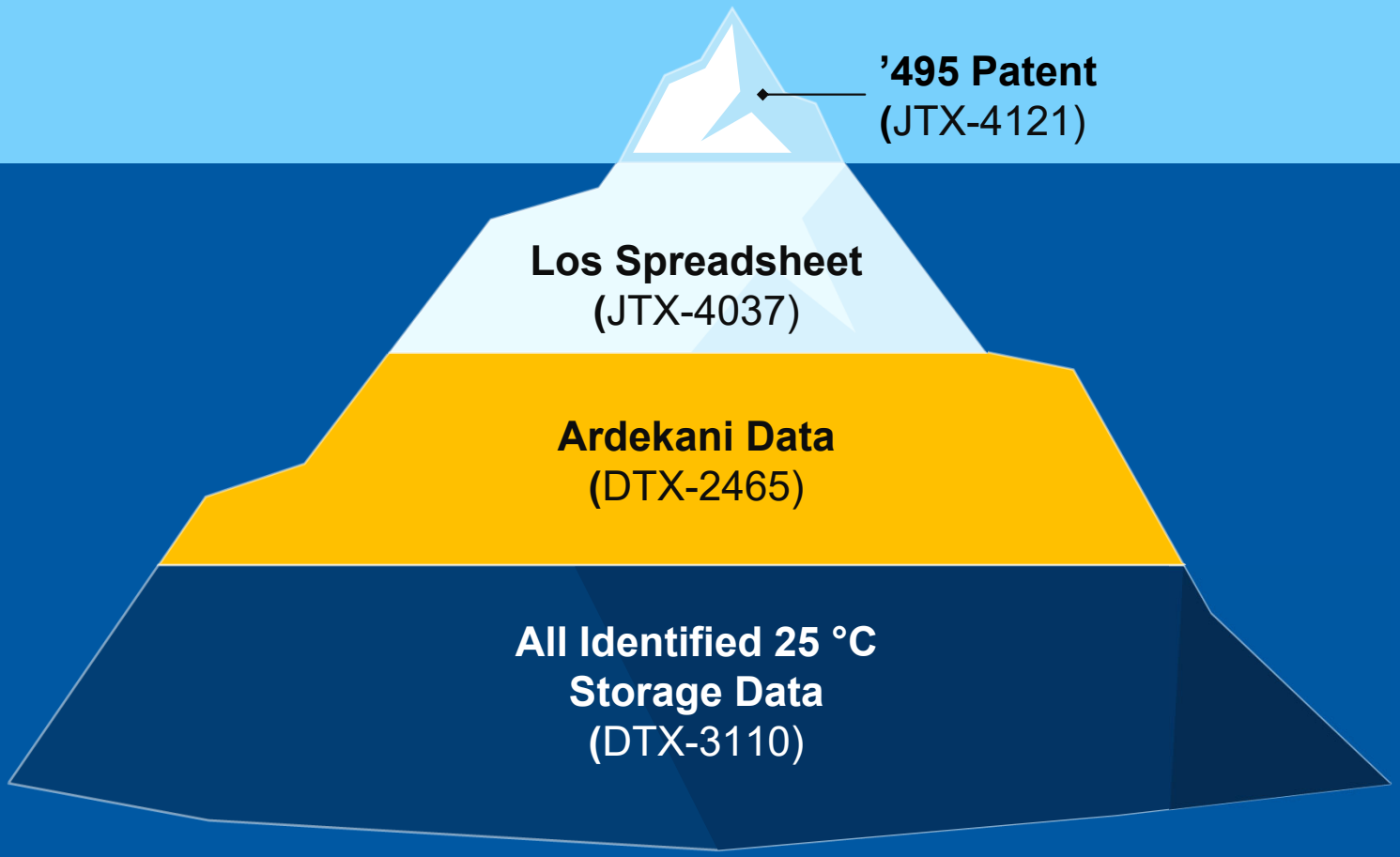
Claims 1, 3, and 5 Are Anticipated by Commercial Batches in the Los Spreadsheet



45L SCC	Lot	0	1m	2m	3m	6m
	20-3066	ND	28	35	52	NA
	20-3067	28	41	57	75	NA
	20-4076	27	43	59	70	NA
	16-p004-pool	ND	LT 20	36	51	111
	16-3088-200	ND	25	35	53	110
	16-3089-200	ND	LT 20	34	54	111
	16-3090-200	ND	LT 20	36	54	114
	17-3142	LT 20	29	43	58	114
	17-4135	LT 20	25	39	54	109
	17-4136	LT 20	34	48	64	123
Average			28.3	38.7	55.4	113.1
% RSD			26.2	24.3	15.0	4.2

JTX-4037.18

Pacira's 45-L Data



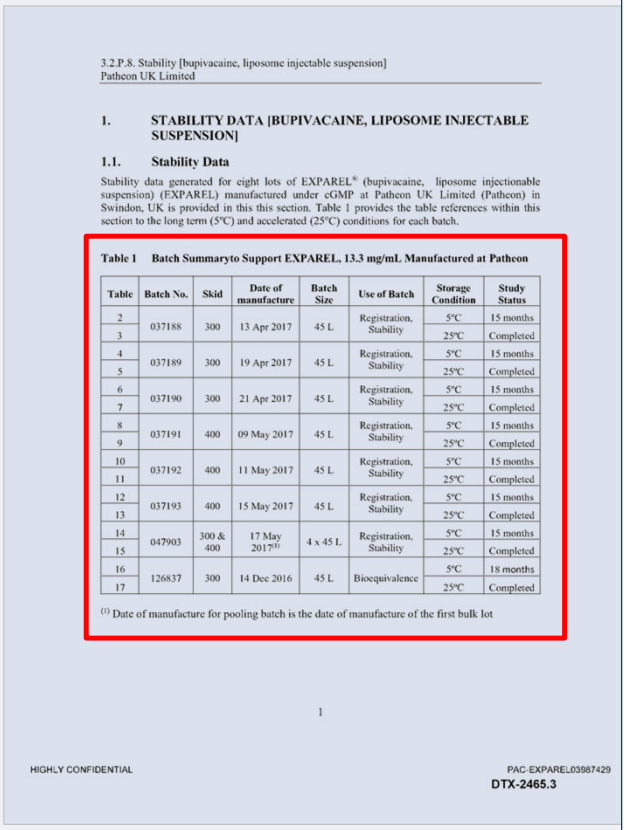
Erucic Acid Stability Data: Ardekani Data

To: Louie Garcia[Louie.Garcia@pacira.com]; Kathy Los[Kathy.Los@pacira.com]
Cc: Paige Davis[Paige.Davis@pacira.com]
From: Soroush Ardekani
Sent: 2020-12-09T18:07:26Z
Importance: Normal
Subject: FW: EXPAREL stability documentation 5 & 25C
Received: 2020-12-09T18:07:37Z
EXPAREL recent stability data.zip

FYI, stability data

DTX-2465.1

Erucic Acid Stability Data: Ardekani Data



3.2.P.8. Stability [bupivacaine, liposome injectable suspension]
Patheon UK Limited

1. STABILITY DATA [BUPIVACAINE, LIPOSOME INJECTABLE SUSPENSION]

1.1. Stability Data

Stability data generated for eight lots of EXPAREL® (bupivacaine, liposome injectionable suspension) (EXPAREL) manufactured under cGMP at Patheon UK Limited (Patheon) in Swindon, UK is provided in this section. Table 1 provides the table references within this section to the long term (5°C) and accelerated (25°C) conditions for each batch.

Table 1 Batch Summaryto Support EXPAREL, 13.3 mg/mL Manufactured at Patheon

Table	Batch No.	Skid	Date of manufacture	Batch Size	Use of Batch	Storage Condition	Study Status
2	037188	300	13 Apr 2017	45 L	Registration, Stability	5°C	15 months
3						25°C	Completed
4	037189	300	19 Apr 2017	45 L	Registration, Stability	5°C	15 months
5						25°C	Completed
6	037190	300	21 Apr 2017	45 L	Registration, Stability	5°C	15 months
7						25°C	Completed
8	037191	400	09 May 2017	45 L	Registration, Stability	5°C	15 months
9						25°C	Completed
10	037192	400	11 May 2017	45 L	Registration, Stability	5°C	15 months
11						25°C	Completed
12	037193	400	15 May 2017	45 L	Registration, Stability	5°C	15 months
13						25°C	Completed
14	047903	300 & 400	17 May 2017(1)	4 x 45 L	Registration, Stability	5°C	15 months
15						25°C	Completed
16	126837	300	14 Dec 2016	45 L	Bioequivalence	5°C	18 months
17						25°C	Completed

(1) Date of manufacture for pooling batch is the date of manufacture of the first bulk lot

1

HIGHLY CONFIDENTIAL

PAC-EXPAREL03987429
DTX-2465.3

DTX-2465.3

Table 1 Batch Summaryto Support EXPAREL, 13.3 mg/mL Manufactured at Patheon

Table	Batch No.	Skid	Date of manufacture	Batch Size	Use of Batch	Storage Condition	Study Status
2	037188	300	13 Apr 2017	45 L	Registration, Stability	5°C	15 months
3						25°C	Completed
4	037189	300	19 Apr 2017	45 L	Registration, Stability	5°C	15 months
5						25°C	Completed
6	037190	300	21 Apr 2017	45 L	Registration, Stability	5°C	15 months
7						25°C	Completed
8	037191	400	09 May 2017	45 L	Registration, Stability	5°C	15 months
9						25°C	Completed
10	037192	400	11 May 2017	45 L	Registration, Stability	5°C	15 months
11						25°C	Completed
12	037193	400	15 May 2017	45 L	Registration, Stability	5°C	15 months
13						25°C	Completed
14	047903	300 & 400	17 May 2017(1)	4 x 45 L	Registration, Stability	5°C	15 months
15						25°C	Completed
16	126837	300	14 Dec 2016	45 L	Bioequivalence	5°C	18 months
17						25°C	Completed

(1) Date of manufacture for pooling batch is the date of manufacture of the first bulk lot

Erucic Acid Stability Data: Ardekani Data

Table 3 Stability Data for EXPAREL, Lot 037188 (25°C) Skid 300

EXPAREL (Bupivacaine Liposome Injectable Suspension), 13.3 mg/mL
Manufacture Date: 13 April 2017
Stability Protocol: 17-STP-002
Stability Start Date: 16 May 2017

Container / Closure:
20-mL Type I clear glass vial
13-mm ETFE-faced grey butyl stopper
13-mm Al/PP flip-off cap
Storage Orientation: Inverted

Attribute		Acceptance criteria	Time Point (Months)				
			0	1	2	3	6
Appearance		White to off-white suspension, free of foreign matter	Complies	Complies (1)	Complies	Complies (1)	Complies
Total Bupivacaine		12.0 to 14.6 mg/mL	13.4	13.4	13.3	13.3	13.5
Free Bupivacaine		NMT 8.0% of label claim	2.7	2.6	2.8	3.2	4.7
Packed Particle Volume (PPV)		32 to 44 %	36	37	36	37	35
Particle size	d_{10}	NLT 12.0 µm	15.2	14.6	14.7	14. 7	14.6
	d_{50}	24.0 to 31.0 µm	27.4	26.7	26.8	26.9	26.7
	d_{90}	NMT 62.0 µm	51.1	50.2	50.6	50.9	50.4
In Vitro Release	4 hours	10 to 35%	21	19	18	19	23
	24 hours	46 to 71%	60	55	53	54	59
	48 hours	60 to 85%	76	72	71	68	77
	168 hours	NLT 80%	94	93	92	93	93
pH		5.8 to 7.4	7.2	7.1	7.1	7.0	6.7
Erucic Acid		NMT 310 µg/mL	ND	23	35	46	90

DTX-2465.5

Erucic Acid Stability Data: Ardekani Data

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	mo.		
1	037188	45L	Skid 300 at Patheon	4/13/2017	25	ND	23	35	46	90	.7	N	JTX-4049.0037
2	037189	45L	Skid 300 at Patheon	4/19/2017	25	ND	25	35	46	89	.8	N	JTX-4049.0038
3	037190	45L	Skid 300 at Patheon	4/21/2017	25	ND	LT20	33	45	83	.8	N	JTX-4049.0039
4	037191	45L	Skid 400 at Patheon	5/9/2017	25	ND	ND	35	44	80	.9	N	JTX-4049.0040
5	037192	45L	Skid 400 at Patheon	5/11/2017	25	ND	ND	35	43	80	.9	N	JTX-4049.0041
6	037193	45L	Skid 400 at Patheon	5/15/2017	25	ND	ND	35	42	78	.9	N	JTX-4049.0042
7	047903	45L	Skid 300 and 400 at Patheon	5/17/2017	25	ND	25	34	43	79	.8	N	JTX-4049.0043 DTX-2512.20
8	126837	45L	Skid 300 at Patheon	12/14/2016	25	ND	LT20	35	41	102	.6	N	JTX-4049.0036 DTX-2519.1

DTX-3110.1; *see* DTX-2465.5, 7, 9, 11, 13, 15, 17, 19

Ms. Los: Aware of Her Obligation to Disclose Data

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. Did you make an attempt to determine the average value across all metric batches before representing to the patent office that the 200-liter process was more stable?

A. I did not make an attempt to collect all of the data for all batches ever manufactured and evaluated. The data requested went back to 2016, so that was a 5-year look back.

Q. Did you understand, Ms. Los, that EXPAREL manufactured prior to 2016 was also prior art to your patent?

A. I did not.

JTX-4289.61 (Los Tr. 266:16-19, 266:23-267:4, 267:8)

Ms. Los: No Distinction Between Sold and Unsold

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. All right. The 45-liter batches in this chart, Ms. Los, were any of those commercial batches?

A. I don't know the nature of those batches.

Q. Did it matter, for the purposes of your comparison, whether they were commercial batches?

A. No. At that time, it did not.

Q. Why not –

A. That wasn't one of our considerations.

Q. Why not?

A. We were working with the stability data that we were provided from regulatory, and we didn't discriminate between them.

Q. Do you think that the batches that you used are representative of what the values would be for commercial batches?

A. Yes, I do. I have no reason to think they wouldn't be.

JTX-4289.23-24 (Los Tr. 124:25-125:15, 125:17-18)

Ms. Los: No Distinction Between Sold and Unsold

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. So, Ms. Los, you'd expect that batches manufactured at a particular location on a particular skid, according to the 45-liter commercial process, are as a general matter representative of the commercial product manufactured on those skids; right?

A. Yeah, I believe so. I'm sure – there is some scatter around some of the measurements, but any – any batch or series of batches should be representative of the – of the process as a whole.

JTX-4289.40 (Los Tr. 184:24-185:4, 185:6-9)

But-for Materiality: Information Contradictory to Applicant's Arguments to USPTO

"The district court appears to have concluded that the [prior art product] could not be found but-for material because it 'was disclosed to' the PTO…. [H]owever, [] the district court found [applicants] 'misrepresented the characteristics of the [product]' by describing it falsely to the PTO… and by withholding a video showing that [it] 'does in fact [practice certain claim limitations].' On remand… the district court must evaluate whether the PTO's patentability decision may have differed if [applicants] had described the [product] accurately and had disclosed the withheld video to the PTO."

Luv n' Care, Ltd. v. Laurain, 98 F.4th 1081, 1097–98 (Fed. Cir. 2024) (citations omitted)

"We further reject Belcher's argument that the withheld art, including the JHP product, is immaterial because it is 'cumulative'… Belcher's argument is directly at odds with its argument during prosecution that the claimed range was 'critical,' which is one way to circumvent obviousness when a claimed range overlaps with a range disclosed in the prior art. The examiner allowed the claims only after accepting Belcher's criticality argument."

Belcher Pharms., LLC v. Hospira, 11 F.4th 1345, 1353 (Fed. Cir. 2013) (quotes and citations omitted)

"By making the comparison [between the claimed range and prior art range] at different dosages without disclosing that this was so, Aventis led the examiner away from any questions about dosage or any motivation to question the dosage for the [prior art] data…. The withholding of the [prior art] dosage information prevented the examiner from considering information important in deciding whether to allow the application, and was therefore a failure to disclose material information to the PTO."

Aventis Pharma S.A. v. Amphastar Pharms., Inc., 176 F. App'x 117, 119–22 (Fed. Cir. 2006)

Materiality: Egregious Misconduct

"When the patentee has engaged in affirmative acts of egregious misconduct … the misconduct is material."

Therasense, Inc. v. Becton, Dickinson & Co., 649 F.3d 1276, 1291-92 (Fed. Cir. 2011) (en banc)

Inequitable Conduct – "n/a" in Table 1A

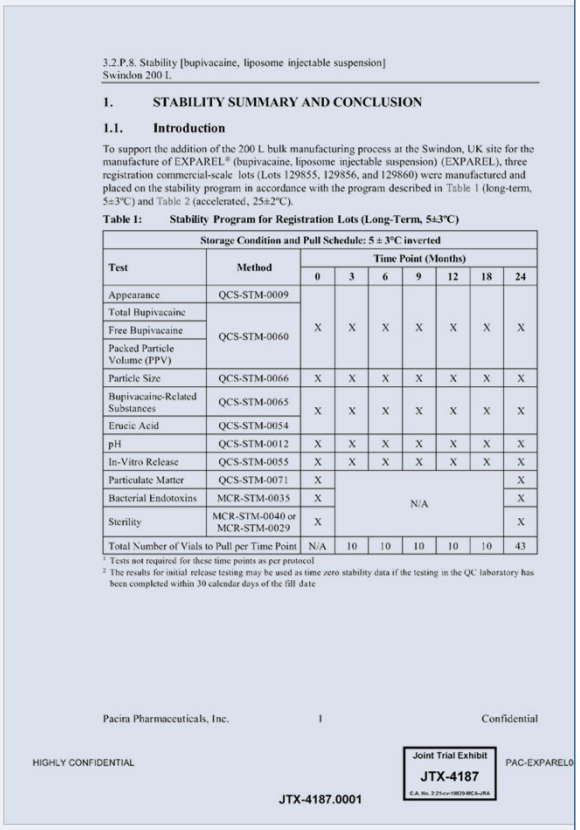
TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

JTX-4121.19, Table 1A at 20:47-67

Pacira's Representations to FDA



3.2.P.8. Stability [bupivacaine, liposome injectable suspension]
Swindon 200 L

1. STABILITY SUMMARY AND CONCLUSION

1.1. Introduction

To support the addition of the 200 L bulk manufacturing process at the Swindon, UK site for the manufacture of EXPAREL® (bupivacaine, liposome injectable suspension) (EXPAREL), three registration commercial-scale lots (Lots 129855, 129856, and 129860) were manufactured and placed on the stability program in accordance with the program described in Table 1 (long-term, 5±3°C) and Table 2 (accelerated, 25±2°C).

Table 1: Stability Program for Registration Lots (Long-Term, 5±3°C)

Storage Condition and Pull Schedule: 5 ± 3°C inverted								
Test	Method	Time Point (Months)						
		0	3	6	9	12	18	24
Appearance	QCS-STM-0009	X	X	X	X	X	X	X
Total Bupivacaine	QCS-STM-0060							
Free Bupivacaine								
Packed Particle Volume (PPV)								
Particle Size	QCS-STM-0066	X	X	X	X	X	X	X
Bupivacaine-Related Substances	QCS-STM-0065	X	X	X	X	X	X	X
Erucic Acid	QCS-STM-0054							
pH	QCS-STM-0012	X	X	X	X	X	X	X
In-Vitro Release	QCS-STM-0055	X	X	X	X	X	X	X
Particulate Matter	QCS-STM-0071	X	N/A					X
Bacterial Endotoxins	MCR-STM-0035	X						X
Sterility	MCR-STM-0040 or MCR-STM-0029	X						X
Total Number of Vials to Pull per Time Point		N/A	10	10	10	10	10	43

[1] Tests not required for these time points as per protocol
[2] The results for initial release testing may be used as time zero stability data if the testing in the QC laboratory has been completed within 30 calendar days of the fill date

Pacira Pharmaceuticals, Inc. 1 Confidential

HIGHLY CONFIDENTIAL

Joint Trial Exhibit JTX-4187 C.A. No. 2:21-cv-19829-MCA-JRA

PAC-EXPAREL0

JTX-4187.0001

JTX-4187.4

1.3.2. Accelerated Storage Conditions (25±2°C)

The stability profile of 20 mL EXPAREL registration lots manufactured using the 200 L bulk manufacturing process is comparable to other EXPAREL lots on the stability program manufactured at the 45 L scale.

At accelerated storage conditions (25±2°C) no significant change in total bupivacaine and bupivacaine related substances was observed at any time point.

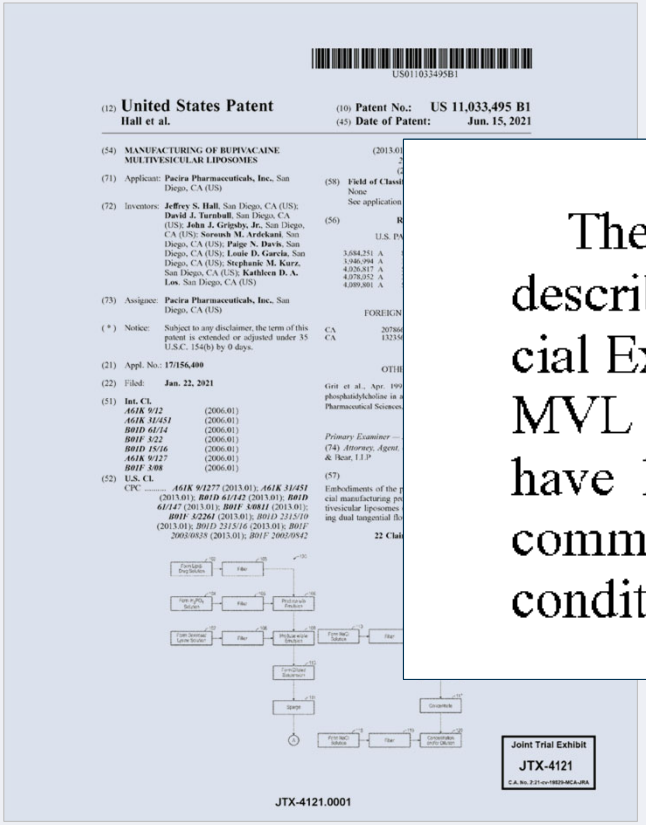
The observed increase in % free bupivacaine, the associated small reduction in packed particles volume (PPV), and the increase in erucic acid are consistent with EXPAREL lots on the stability program manufactured at the 45 L scale over 6 months.

A small decrease in pH values was observed over 6 months but they were within the expected range and associated with the slight increase in percentage of free bupivacaine. The trend is consistent with other EXPAREL lots placed on the stability program at accelerated storage conditions (25±2°C).

An increase in particle size distribution at d_{90} was observed at 6 months for all registration lots. The trend is consistent with other EXPAREL lots placed on the stability program at accelerated storage conditions (25±2°C).

For in-vitro release, all registration lots were slightly above the range 60 – 85% at 48 hours. The trend is consistent with other EXPAREL lots placed on the stability program at accelerated storage conditions (25±2°C).

’495 Patent – Affirmative Misstatements



US011033495B1

(12) **United States Patent**
Hall et al.

(10) **Patent No.: US 11,033,495 B1**
(45) **Date of Patent: Jun. 15, 2021**

(54) **MANUFACTURING OF BUPIVACAINE MULTIVESICULAR LIPOSOMES**

(71) Applicant: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(72) Inventors: **Jeffrey S. Hall**, San Diego, CA (US); **David J. Turnbull**, San Diego, CA (US); **John J. Grigsby, Jr.**, San Diego, CA (US); **Soroush M. Ardekani**, San Diego, CA (US); **Paige N. Davis**, San Diego, CA (US); **Louie D. Garcia**, San Diego, CA (US); **Stephanie M. Kurz**, San Diego, CA (US); **Kathleen D. A. Lee**, San Diego, CA (US)

(73) Assignee: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/156,400**

(22) Filed: **Jan. 22, 2021**

(51) **Int. Cl.**
A61K 9/12 (2006.01)
A61K 31/451 (2006.01)
B01D 61/14 (2006.01)
B01F 1/22 (2006.01)
B01D 15/16 (2006.01)
A61K 9/127 (2006.01)
B01F 1/08 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 9/1277*** (2013.01); ***A61K 31/451*** (2013.01); ***B01D 61/142*** (2013.01); ***B01D 61/147*** (2013.01); ***B01F 1/0811*** (2013.01); ***B01F 1/2261*** (2013.01); ***B01D 2315/10*** (2013.01); ***B01D 2315/16*** (2013.01); ***B01F 2003/0838*** (2013.01); ***B01F 2002/0842***

(58) **Field of Classi**
None
See application

(56) **R**

U.S. PA

3,684,251 A
3,946,994 A
4,026,817 A
4,078,052 A
4,089,801 A

FOREIGN

CA 207866
CA 132354

OTHE

Grit et al., Apr. 199
phosphatidylcholine in a
Pharmaceutical Sciences,

Primary Examiner —
(74) *Attorney, Agent,*
& Bear, LLP

(57)

Embodiments of the p
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22 Clai

Joint Trial Exhibit
JTX-4121

JTX-4121.0001

The bupivacaine MVLs produced by the process described herein have improved stability over the commercial Exparel® product. It was observed that the bupivacaine MVL particles produced by the process described herein have lower lipid hydrolysis byproducts compared to the commercial Exparel® product under the same incubation condition. In addition, the bupivacaine MVL particles pro-

JTX-4121.16 at 13:49-55

’495 Patent File History – Applicant Amendment and Response

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 15, 2022

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *17/156,400*
FILING DATE: *January 22, 2021*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

John Burson
Certifying Officer

Joint Trial Exhibit
JTX-4001

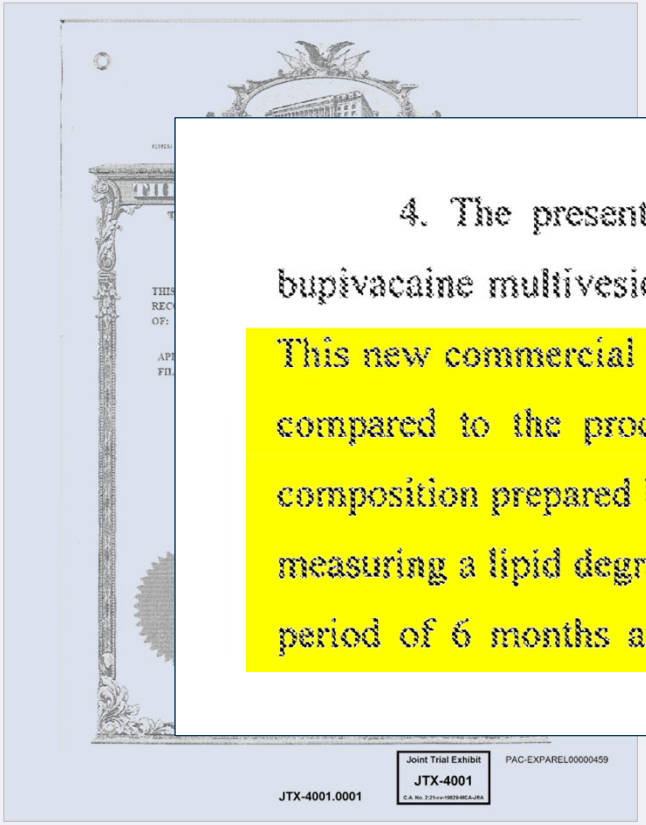
JTX-4001.0001

The cited references fail to teach all the claimed features in instant claim 1.

The present claims are directed to bupivacaine MVL compositions prepared by a newly developed commercial process. This new commercial process yields a bupivacaine MVL product with superior stability as compared to the product made by the prior process. In particular, the bupivacaine MVLs composition prepared by the new process has demonstrated less lipid membrane degradation, as measured by a lipid degradation byproduct erucic acid in the bupivacaine MVLs suspension over a period of 6 months at 25°C. *See* Los Declaration at paragraph 4. The bupivacaine MVLs manufactured by the claimed process has a target concentration of bupivacaine from about 12.6 mg/mL to about 17.0 mg/mL and can be directly administered to a patient without further purification. *Id.* In addition, instant claim 1 recites, in part, “wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25°C for one month.” These features are not expressly disclosed in either Camu or Li. Furthermore, the Office Action has not provided any evidence to demonstrate that these recited features are inherently present in either Camu or Li. As such, a *prima facie* case of obviousness has not been established at least because each and every claim limitation is not disclosed in the cited references.

JTX-4001.2176

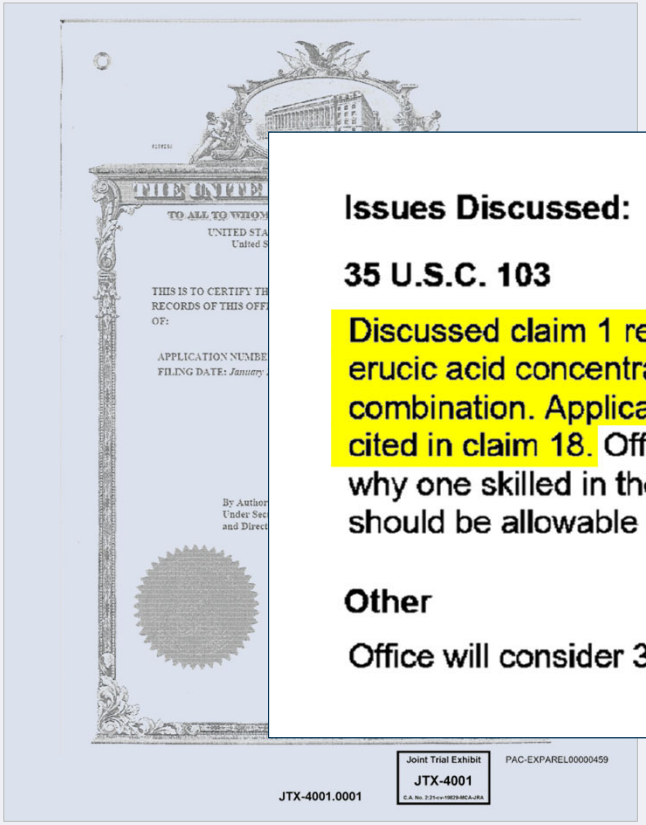
’495 Patent File History – Los Declaration



4. The present application is directed to a 200L commercial scale manufacturing of bupivacaine multivesicular liposomes (MVLs), a project which we started developing in 2013. This new commercial process yields a bupivacaine MVL composition with superior stability as compared to the product made by the prior process. In particular, the bupivacaine MVLs composition prepared by the new process has demonstrated less lipid membrane degradation, by measuring a lipid degradation byproduct erucic acid in the bupivacaine MVLs suspension over a period of 6 months at 25°C. Erucic acid is a degradation product of dierucoyl phosphatidyl

JTX-4001.2179

’495 Patent File History – Summary of Interview



Issues Discussed:

35 U.S.C. 103

Discussed claim 1 rejection and Applicants argued that the combination does not teach the amount of erucic acid concentration after one month as the product by process is more stable than the cited art combination. Applicant further argues that the process allows higher concentrations of bupivacaine as cited in claim 18. Office indicated that adding claims 17 and 18 to claim 1 and providing a declaration of why one skilled in the art would not expect the prior art to have the same claimed acid concentration should be allowable after a final search and consideration of the 3/12/2021 ids.

Other

Office will consider 3/12/2021 ids in next action

JTX-4001.2167

'495 Patent File History – Applicant Amendment and Response

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 15, 2022

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *17/156,400*
FILING DATE: *January 22, 2021*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

John Burson
Certifying Officer

Joint Trial Exhibit
JTX-4001

JTX-4001.0001

The cited references fail to teach all the claimed features in instant claim 1.

The present claims are directed to bupivacaine MVL compositions prepared by a newly developed commercial process. This new commercial process yields a bupivacaine MVL product with superior stability as compared to the product made by the prior process. In particular, the bupivacaine MVLs composition prepared by the new process has demonstrated less lipid membrane degradation, as measured by a lipid degradation byproduct erucic acid in the bupivacaine MVLs suspension over a period of 6 months at 25°C. *See* Los Declaration at paragraph 4. The bupivacaine MVLs manufactured by the claimed process has a target concentration of bupivacaine from about 12.6 mg/mL to about 17.0 mg/mL and can be directly administered to a patient without further purification. *Id.* In addition, instant claim 1 recites, in part, "wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25°C for one month." These features are not expressly disclosed in either Camu or Li. Furthermore, the Office Action has not provided any evidence to demonstrate that these recited features are inherently present in either Camu or Li. As such, a *prima facie* case of obviousness has not been established at least because each and every claim limitation is not disclosed in the cited references.

JTX-4001.2176

Inequitable Conduct: Intent

Inequitable Conduct

"'[B]ecause direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence,' provided that such intent is the single reasonable inference."

Am. Calcar, Inc. v. Am. Honda Motor Co., Inc., 768 F.3d 1185, 1190-91 (Fed. Cir. 2014) (quoting *Therasense,* 649 F.3d 1276, 1290-91 (Fed Cir. 2011))

Mr. Molloy: Pacira's Inventors Know the Duty of Candor

Anthony Molloy

PACIRA PHARMACEUTICALS, INC.

Q. Now, Mr. Molloy, as the person in charge of the IP portfolio at Pacira, you also take charge to make sure that you educate inventors about the duty of candor, right?

A. Yes.

Q. They understand – the inventors are taught the ethical duties that they have during the prosecution, right?

A. That's right.

***

Q. You'll agree with me that Pacira makes the scientists and inventors aware of the duty of candor?

A. Absolutely.

Tr. 333:9-15, 333:24-334:1 (Molloy)

Ms. Los: Aware of Her Duty to Disclose Data

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. And what is your own personal understanding of your duty of candor to the patent office as an inventor?

A. That I would not – in this situation, I guess – withhold data that was relevant to what the patent was about. Mainly that.

***

Q. So fair to say, in the general sense – not related to the specific prosecution of these patents – that if you were aware of a document or data that you thought was potentially important, you would tell your lawyers and expect them to determine whether it went to the patent office?

A. That's correct.

JTX-4289.41-42 (Los Tr. 190:22-191:2, 192:15-20, 192:22)

Ms. Los: Aware of Her Duty to Disclose Data

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. When you testified earlier that the duty of candor includes not withholding data that is relevant to what the patent is about, is your understanding that that includes internal data about prior art commercial products?

A. I'm – yeah, I guess not. At least, not to the scope I – full scope.

Q. Sorry, what do you mean by "I guess not"?

A. Well, as I've tried to explain, our role – my role and the role of my colleagues in the formulation development group has been to perform the analyses accurately, provide the data in full. With regard to understanding of the rules surrounding what does or doesn't get included, we count on our patent prosecution attorneys to make those interpretations.

JTX-4289.42 (Los Tr. 191:19-23, 192:2-4, 192:7-14)

Ms. Los: Aware of Her Duty of Candor

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. Do you understand that you have a duty [to] be honest with the patent office?

A. Yes.

***

Q. Do you have an understanding as to whether or not your duty of candor allows you to mislead the patent office?

A. I – yes, I would have to – I would conclude that the duty of candor would of course include not intentionally misleading the patent office.

JTX-4289.41, 43 (Los Tr. 191:3-5, 193:16-18, 192:21-24)

Dr. Dai: Aware of Her Duty to Disclose Prior Art

Dr. Jane Dai

Q. While prosecuting the asserted patents, did you understand that you had a duty to disclose material prior art to the patent office?

A. Yes.

Q. While prosecuting the asserted patents, did you understand that Exparel had been commercially marketed since 2012?

A. I was aware Exparel was being marketed prior to the patent – filing of the patent, but I do not know the exact year that it was proved.

Q. While prosecuting the asserted patents, did you understand that prior commercial sales of a product could constitute prior art?

A. Yes.

JTX-4288.13-14
(Dai Tr. 129:10-16, 129:22-130:3)

Dr. Dai: No Explanation Why Individual Data Was Withheld

Dr. Jane Dai

Q. Why was the data, on individual batches of 45-liter Exparel in Exhibit 7 [the Los Spreadsheet], not provided to the patent office, during prosecution of the asserted patents?

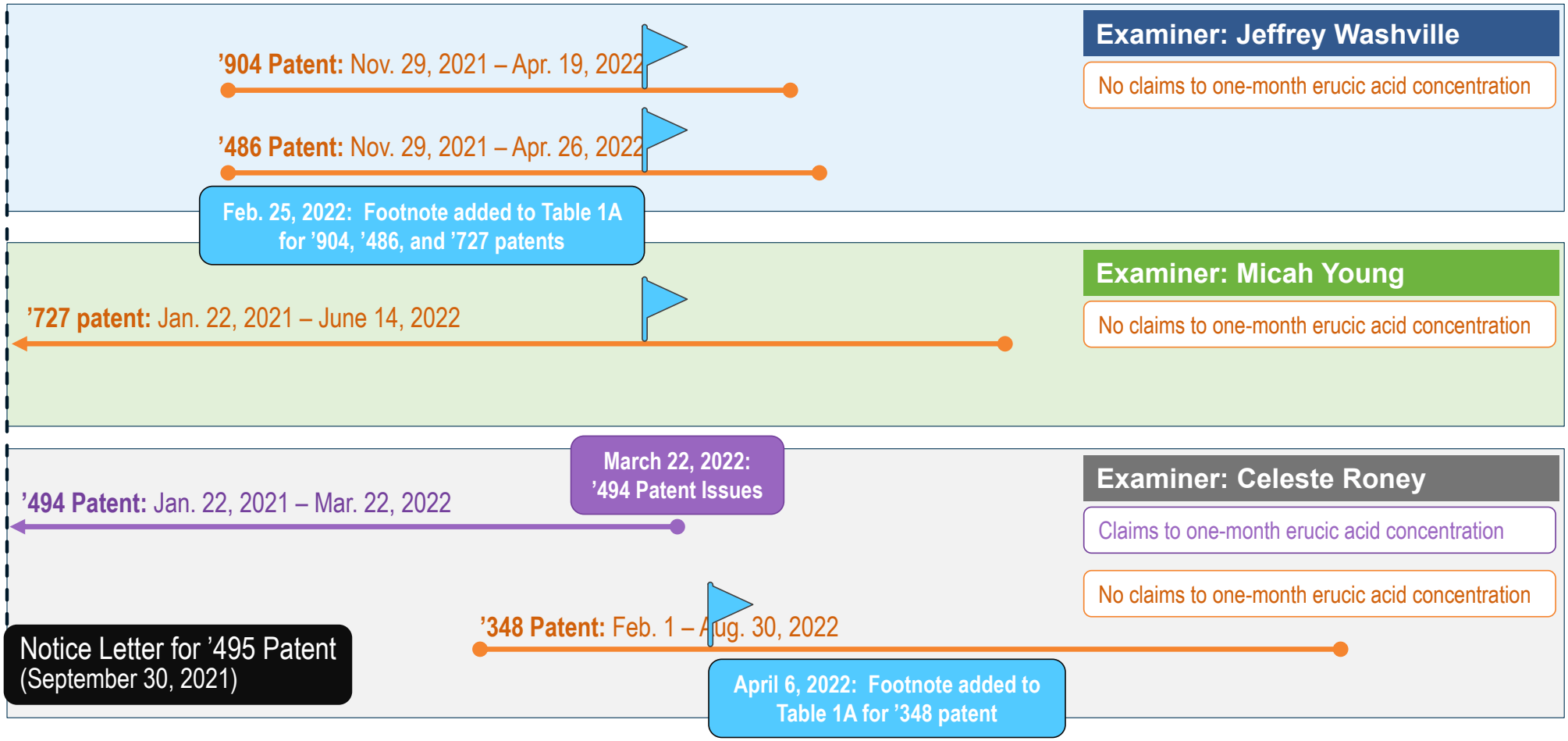
MR. SINGER: Objection. This question has been asked multiple times already. I instruct the witness not to answer, as based on attorney-client privilege.

Q. Are you going to follow your counsel's instructions?

A. Yes.

JTX-4288.12-13 (Dai Tr. 127:16-128:1)

Prosecution of Related Patents: Timeline



DTX-3118

Intent to Deceive Inferred When:

"Mr. Rubin … understood that [patentee] had stated to the FDA that the 2.8 to 3.3 pH range was an 'old' range. Mr. Rubin also understood that [patentee] had reverted from its original pH range (2.4 to 2.6) to the 2.8 to 3.3 range because … using that range would expedite FDA approval. When later drafting the patent application and through his communications with the PTO during prosecution, however, Mr. Rubin performed an about-face and emphatically and repeatedly advanced the position that the 2.8 to 3.3 pH range was a 'critical' innovation contrary to the knowledge of a person of ordinary skill in the art that yielded 'unexpected results' …. [T]his argument was 'false' and a 'fiction' because Mr. Rubin knew about the prior art's teachings of that pH range."

Belcher Pharms., LLC v. Hospira, 11 F.4th 1345, 1353 (Fed. Cir. 2021) (internal citations omitted)

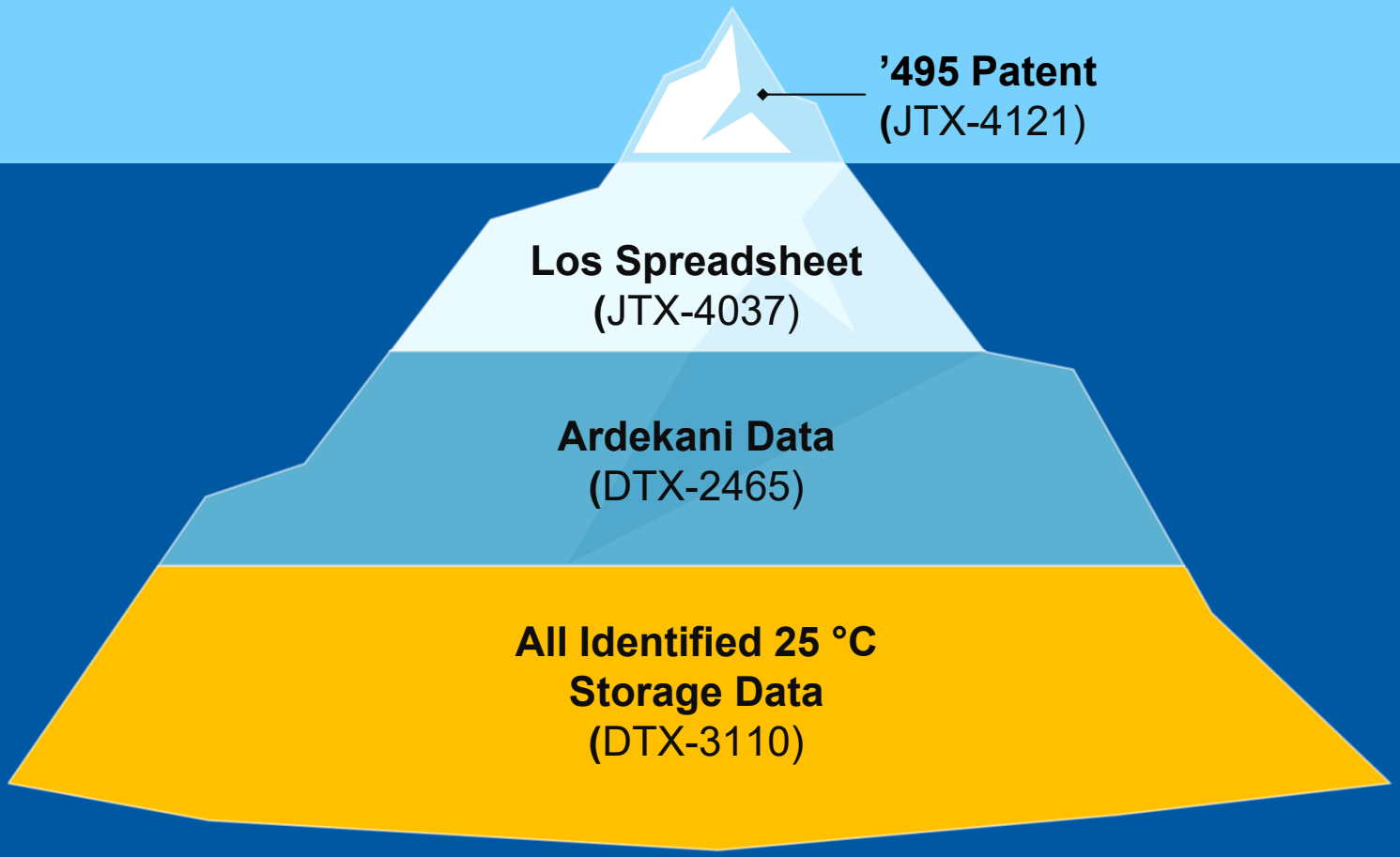
Consideration of Pattern of Conduct to Infer Intent

"Acts which are not per se unreasonable when considered in isolation may still demonstrate repeated attempts to avoid playing fair and square with the patent system and, collectively, support a finding of deceptive intent. When a person having a duty of candor and good faith has engaged in serial misconduct during the prosecution of the same or related patents, it is not enough for a court to consider each individual act of misconduct without also considering the collective whole. Because an intent to deceive the PTO can be inferred from a person's pattern of lack of candor, a district court must consider the person's multiple acts of misconduct in the aggregate."

Luv n' Care, Ltd. v. Laurain, 98 F.4th 1081, 1098 (Fed. Cir. 2024)
(quotes and citations omitted)

Anticipation

Pacira's 45-L Data



Pacira's Accelerated (25 °C) Stability Data

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhi
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
1	037188	45L	Skid 300 at Patheon	4/13/2017	25	ND	23	35	46	90	6.7	N	JTX-4049
2	037189	45L	Skid 300 at Patheon	4/19/2017	25	ND	25	35	46	89	6.8	N	JTX-4049
3	037190	45L	Skid 300 at Patheon	4/21/2017	25	ND	LT20	33	45	83	6.8	N	JTX-4049
4	037191	45L	Skid 400 at Patheon	5/9/2017	25	ND	ND	35	44	80	6.9	N	JTX-4049
5	037192	45L	Skid 400 at Patheon	5/11/2017	25	ND	ND	35	43	80	6.9	N	JTX-4049
6	037193	45L	Skid 400 at Patheon	5/15/2017	25	ND	ND	35	42	78	6.9	N	JTX-4049
7	047903	45L	Skid 300 and 400 at Patheon	5/17/2017	25	ND	25	34	43	79	6.8	N	JTX-4049 DTX-251
8	126837	45L	Skid 300 at Patheon	12/14/2016	25	ND	LT20	35	41	102	6.6	N	JTX-4049 DTX-251
9	13-2204	45L	Suite C (Skid 200)	7/11/2013	25	ND	ND	22	36	93	6.7	N	JTX-4049 DTX-251
10	13-2205	45L	Suite C (Skid 200)	7/13/2013	25	ND	LT20	23	35	91	6.7	N	JTX-4049 DTX-251
11	13-2206	45L	Suite C (Skid 200)	7/15/2013	25	ND	LT20	24	37	92	6.7	N	JTX-4049 DTX-251
12	14-2107	45L	Suite A	4/26/2014	25	21	38	57	79	146	6.3	N	JTX-4051
13	14-4001	45L	Suite C (Skid 100)	3/25/2014	25	ND	20	41	58	127	6	N	JTX-4049 DTX-251
14	14-4004	45L	Suite C (Skid 100)	3/31/2014	25	ND	21	42	57	125	6.1	N	JTX-4049 DTX-251
15	14-4005	45L	Suite C (Skid 100)	4/2/2014	25	LT20	22	40	56	122	6.3	N	JTX-4049 DTX-251
16	14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049
17	14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049
18	14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049
19	14-P002	45L	Suite C	4/8/2014	25	ND	22	42	63	135	6.3	N	JTX-4051
20	14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	41	53	118	6.4	Y	JTX-4049
21	15 3138	45L	Suite C (Skid 200)	7/2/2015	25	ND	LT20	35	54	116	6.2	N	JTX 4049
22	15-3139	45L	Suite C (Skid 200)	7/2/2015	25	ND	LT20	36	53	113	6.1	N	JTX-4049
23	15-4126	45L	Suite C (Skid 100)	7/2/2015	25	ND	LT20	35	51	115	6.5	N	JTX-4049
24	16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049
25	16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049 JTX-4079
26	16-3090	45L	Suite C (Skid 200)	6/9/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049
27	16-P004	45L	Suite C Pooling	6/15/2016	25	ND	LT20	36	51	111	6.5	N	JTX-4049
28	17-3142	45L	Suite C (Skid 200)	7/4/2017	25	LT20	29	43	58	114	6.4	N	JTX-4049
29	17-4135	45L	Suite C (Skid 100)	7/3/2017	25	LT20	25	39	54	109	6.5	N	JTX-4049
30	17-4136	45L	Suite C (Skid 100)	7/4/2017	25	LT20	34	48	64	123	6.5	N	JTX-4049
31	18-3010	45L	Suite C (Skid 200)	2/10/2018	25	LT20	29	41	57	107	6.5	N	JTX-4049
32	18-4009	45L	Suite C (Skid 100)	2/9/2018	25	LT20	30	41	58	109	6.6	N	JTX-4049
33	18-4010	45L	Suite C (Skid 100)	2/10/2018	25	LT20	34	46	61	115	6.5	N	JTX-4049

HIGHLY CONFIDENTIAL

2:21-cv-19829
Defendants' Exhibit
DTX-3110

DTX-31

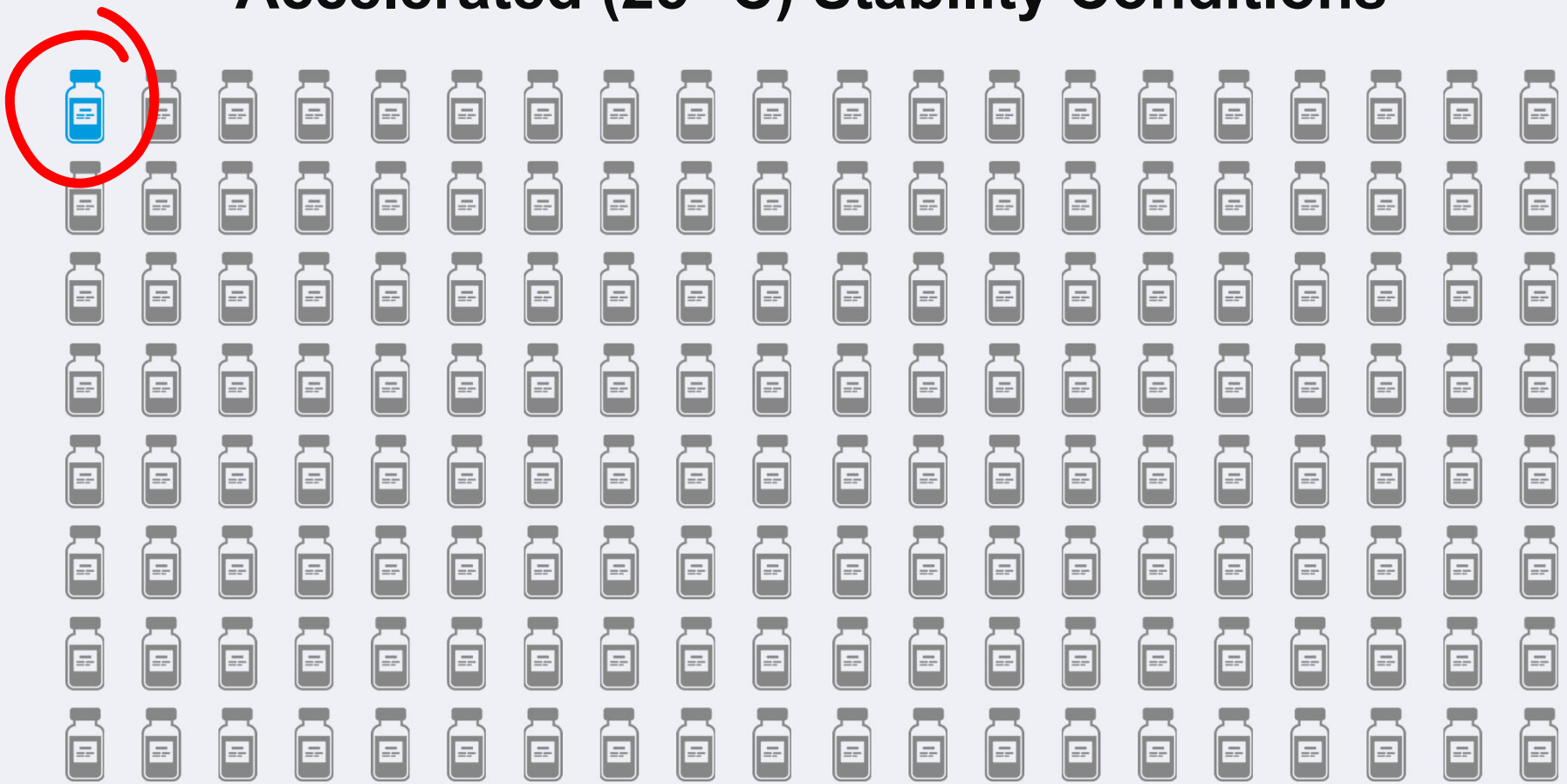
Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
34	18-P002	45L	Suite C (Skid 100 and 200)	6/3/2018	25	LT20	28	40	57	112	6.5	N	JTX-4049.0050 DTX-2512.23
35	18-P003	45L	Suite C (Skid 100 and 200)	6/4/2020	25	LT20	29	42	59	116	6.5	Y	JTX-4049.0051 DTX-2512.23
36	18-P004	45L	Suite C (Skid 100 and 200)	6/5/2020	25	LT20	28	40	56	111	6.5	Y	JTX-4049.0052 DTX-2512.23
37	18-P063	45L	Suite C (Skid 100)	11/29/2020	25	LT20	28	48	62	127	6.5	Y	JTX-4049.0053
38	18-SS-020	45L	Suite C (Skid 100)	6/24/2018	25	LT20	LT20	40	55	98	6.5	N	JTX-4051.0017
39	18-SS-021	45L	Suite C (Skid 100)	6/25/2018	25	LT20	LT20	40	53	99	6.5	N	JTX-4051.0018
40	18-SS-022	45L	Suite C (Skid 200)	6/22/2018	25	LT20	LT20	38	51	93	6.6	N	JTX-4051.0019
41	18-SS-023	45L	Suite C (Skid 200)	6/23/2018	25	LT20	LT20	46	59	107	6.5	N	JTX-4051.0020
42	18-SS-024	45L	Suite C (Skid 200)	6/24/2018	25	LT20	LT20	42	58	100	6.5	N	JTX-4051.0021
43	18-SS-061	45L	Suite C (Skid 100)	10/30/2018	25	ND	LT20	34	62	111	6.5	N	JTX-4051.0022
44	20-3066	45L	Suite C (Skid 200)	3/15/2020	25	ND	28	35	52	101	6.2	N	JTX-4049.0054 DTX-2529.1
45	20-3067	45L	Suite C (Skid 200)	3/16/2020	25	28	41	57	75	128	6.4	N	JTX-4049.0055 DTX-2529.1
46	20-4076	45L	Suite C (Skid 200)	3/22/2020	25	27	43	59	70	125	6.5	N	JTX-4049.0056 DTX-2529.1
47	20-SS-011	45L	Suite C (Skid 100)	3/23/2020	25	LT20	34	49	65	118	6.4	N	JTX-4051.0028 DTX-2372.1 DTX-2525.4 DTX-2524.4
48	18-SS-019	45L	Suite C (Skid 100)	6/23/2018	25	ND	LT20	34	-	-	-	N	JTX-4051.0016
49	18-SS-062	45L	Suite C (Skid 100)	10/31/2018	25	ND	28	35	67	-	-	N	JTX-4051.0023
50	18-SS-063	45L	Suite C (Skid 200)	10/30/2018	25	LT20	27	40	72	-	-	N	JTX-4051.0024
51	18-SS-071	45L	Suite C (Skid 200)	11/20/2018	25	-	-	-	-	-	6.5	N	JTX-4051.0025 DTX-2342.3
52	19 SS 032	45L	Suite C (Skid 100)	7/12/2019	25	LT20		40	54	121	6.5	N	JTX 4051.0026 DTX-2343.1 DTX-2521.2 DTX-2522.2
53	19-SS-052	45L	Suite C (Skid 200)	12/22/2019	25	27	40	56	80	-	-	N	JTX-4051.0027 DTX-2354.1 DTX-2523.2

HIGHLY CONFIDENTIAL

DTX-3110.2

DTX-3110.1-2

Pacira Rarely Tests the Batches it Sells Under Accelerated (25 °C) Stability Conditions



Pacira's Accelerated (25 °C) Stability Data

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C)
of 45 L Commercial Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													

Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
					0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049.0025
14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049.0026
14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049.0027
14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	41	53	118	6.4	Y	JTX-4049.0028
16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049.0033
16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049.0032
16-3090	45L	Suite C (Skid 200)	6/9/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049.0034
18-P003	45L	Suite C (Skid 100 and 200)	6/4/2020	25	LT20	29	42	59	116	6.5	Y	JTX-4049.0051 DTX-2512.23
18-P004	45L	Suite C (Skid 100 and 200)	6/5/2020	25	LT20	28	40	56	111	6.5	Y	JTX-4049.0052 DTX-2512.23
18-P063	45L	Suite C (Skid 100)	11/29/2020	25	LT20	28	48	62	127	6.5	Y	JTX-4049.0053

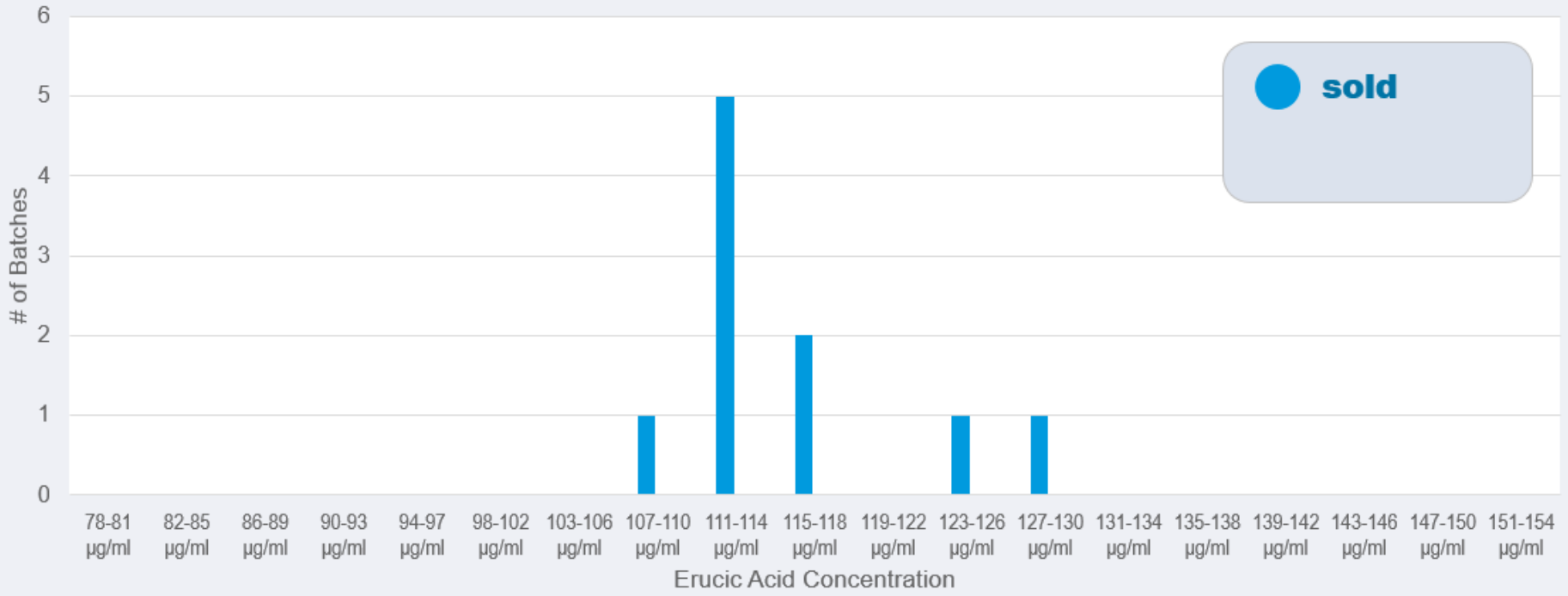
DTX-3111

2:21-cv-19829
Defendants' Exhibit
DTX-3111

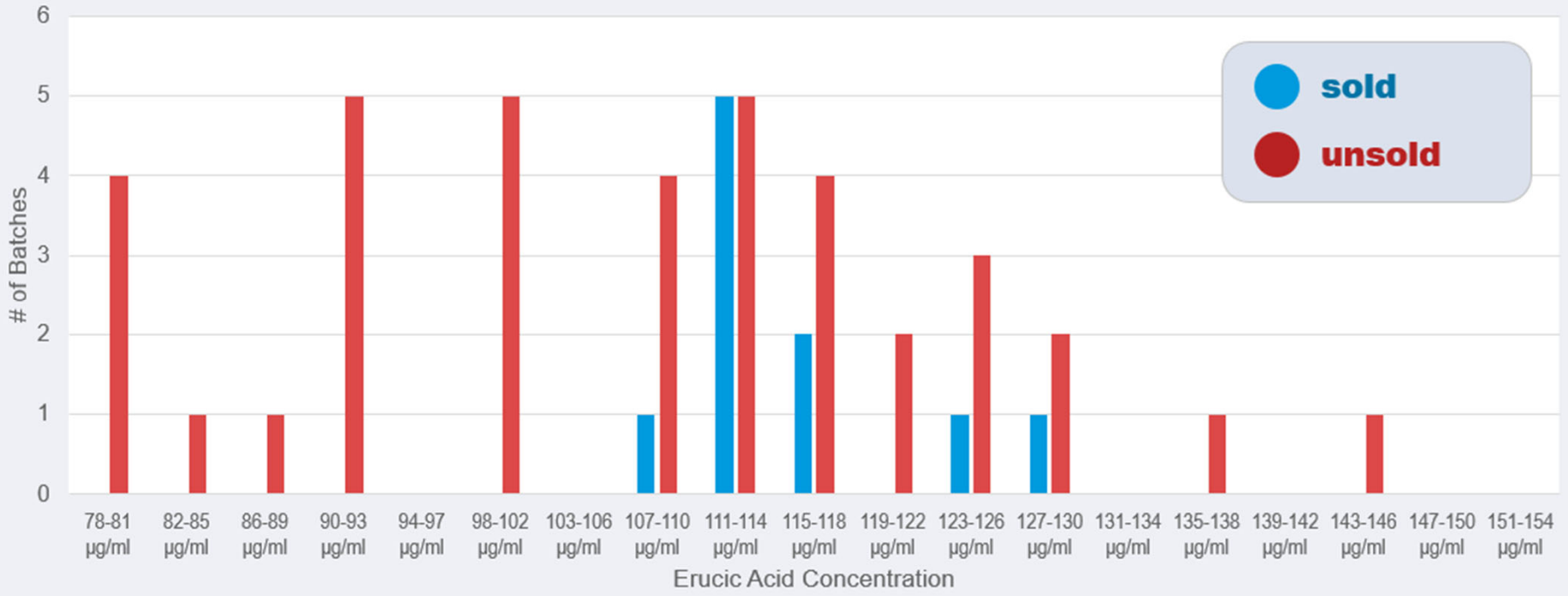
HIGHLY CONFIDENTIAL

DTX-3111.1

45-L Batches – Erucic Acid Concentration after Six Months at 25 °C



45-L Batches – Erucic Acid Concentration after Six Months at 25 °C



Ms. Los: No Distinction Between Sold and Unsold

Kathleen Los

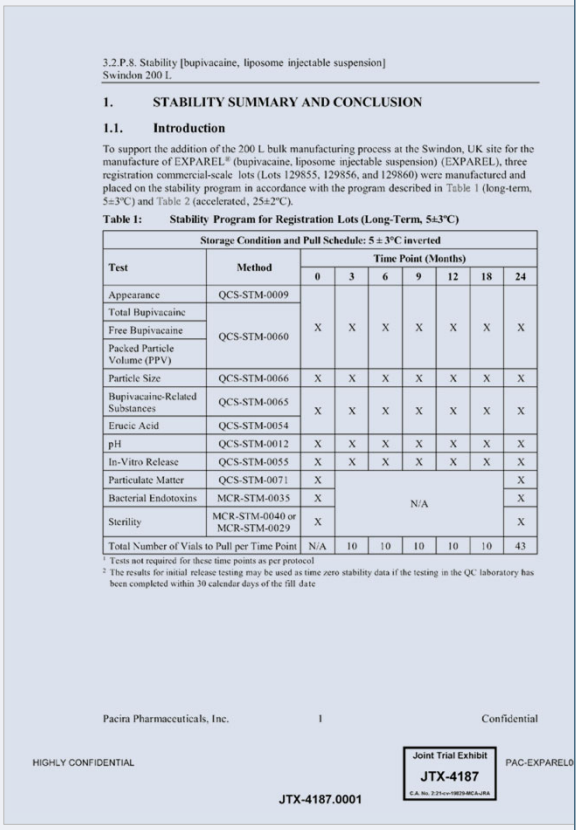
PACIRA PHARMACEUTICALS, INC.

Q. So, Ms. Los, you'd expect that batches manufactured at a particular location on a particular skid, according to the 45-liter commercial process, are as a general matter representative of the commercial product manufactured on those skids; right?

A. Yeah, I believe so. I'm sure – there is some scatter around some of the measurements, but any – any batch or series of batches should be representative of the – of the process as a whole.

JTX-4289.40 (Los Tr. 184:24-185:4, 185:6-9)

Pacira's Representations to FDA



3.2.P.8. Stability [bupivacaine, liposome injectable suspension]
Swindon 200 L

1. STABILITY SUMMARY AND CONCLUSION

1.1. Introduction

To support the addition of the 200 L bulk manufacturing process at the Swindon, UK site for the manufacture of EXPAREL® (bupivacaine, liposome injectable suspension) (EXPAREL), three registration commercial-scale lots (Lots 129855, 129856, and 129860) were manufactured and placed on the stability program in accordance with the program described in Table 1 (long-term, 5±3°C) and Table 2 (accelerated, 25±2°C).

Table 1: Stability Program for Registration Lots (Long-Term, 5±3°C)

Storage Condition and Pull Schedule: 5 ± 3°C inverted								
Test	Method	Time Point (Months)						
		0	3	6	9	12	18	24
Appearance	QCS-STM-0009	X	X	X	X	X	X	X
Total Bupivacaine	QCS-STM-0060							
Free Bupivacaine								
Packed Particle Volume (PPV)								
Particle Size	QCS-STM-0066	X	X	X	X	X	X	X
Bupivacaine-Related Substances	QCS-STM-0065	X	X	X	X	X	X	X
Erucic Acid	QCS-STM-0054							
pH	QCS-STM-0012	X	X	X	X	X	X	X
In-Vitro Release	QCS-STM-0055	X	X	X	X	X	X	X
Particulate Matter	QCS-STM-0071	X	N/A					X
Bacterial Endotoxins	MCR-STM-0035	X						X
Sterility	MCR-STM-0040 or MCR-STM-0029	X						X
Total Number of Vials to Pull per Time Point		N/A	10	10	10	10	10	43

[1] Tests not required for these time points as per protocol
[2] The results for initial release testing may be used as time zero stability data if the testing in the QC laboratory has been completed within 30 calendar days of the fill date

Pacira Pharmaceuticals, Inc. 1 Confidential

HIGHLY CONFIDENTIAL

Joint Trial Exhibit JTX-4187 C.A. No. 2:21-cv-19829-MCA-JRA

PAC-EXPAREL0

JTX-4187.0001

JTX-4187.4

1.3.2. Accelerated Storage Conditions (25±2°C)

The stability profile of 20 mL EXPAREL registration lots manufactured using the 200 L bulk manufacturing process is comparable to other EXPAREL lots on the stability program manufactured at the 45 L scale.

At accelerated storage conditions (25±2°C) no significant change in total bupivacaine and bupivacaine related substances was observed at any time point.

The observed increase in % free bupivacaine, the associated small reduction in packed particles volume (PPV), and the increase in erucic acid are consistent with EXPAREL lots on the stability program manufactured at the 45 L scale over 6 months.

A small decrease in pH values was observed over 6 months but they were within the expected range and associated with the slight increase in percentage of free bupivacaine. The trend is consistent with other EXPAREL lots placed on the stability program at accelerated storage conditions (25±2°C).

An increase in particle size distribution at d_{90} was observed at 6 months for all registration lots. The trend is consistent with other EXPAREL lots placed on the stability program at accelerated storage conditions (25±2°C).

For in-vitro release, all registration lots were slightly above the range 60 – 85% at 48 hours. The trend is consistent with other EXPAREL lots placed on the stability program at accelerated storage conditions (25±2°C).

Pacira's Proposed Findings of Fact

201. Four of these non-prior art batches (18-SS-020, 18-SS-021, 18-SS-022, 18-SS-024) are European PPQ batches that contained an additional manufacturing step, were removed from the U.S. stability program, and thus could not be sold. (Day 4 at 523:15-21, 526:13-527:7 (Schwendeman); PTX-492.)

202. Three of these non-prior art batches (13-2204, 13-2205, 13-2206) are registration lots that were made at a time when the FDA had not yet approved or qualified the manufacturing line. (Day 4 at 527:17-528:20 (Schwendeman); PTX-492.)

Defendants.

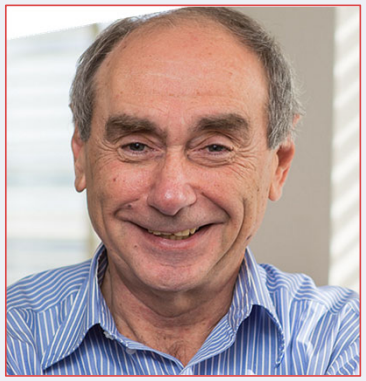
PACIRA PHARMACEUTICALS, INC. AND PACIRA BIOSCIENCES, INC.'S PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW REGARDING VALIDITY AND ENFORCEABILITY OF THE ASSERTED PATENT

D.I. 369-1, ¶¶ 201-04 (Plaintiffs' Proposed Findings of Fact and Conclusions of Law Regarding Invalidity and Enforceability of the Asserted Patent)

203. Five of these non-prior art batches (037188, 037190, 037191, 037192, 037193) are registration stability lots that were similarly made at a time when the FDA had not yet approved or qualified the manufacturing line. (Day 4 at 528:21-529:8 (Schwendeman); PTX-492.)

204. The final non-prior art batch (126837) is a bioequivalence lot that was also made at a time when the FDA had not yet approved or qualified the manufacturing line. (Day 4 at 529:9-13 (Schwendeman); PTX-492.)

Dr. Klibanov: Patent Averages Sold and Unsold Batches



Dr. Alexander Klibanov

Q. Well, you understand that the patent reports averages for 2-, 3-, and 6- month results for the 45-liter batches, correct?

A. That's right.

Q. And those averages include results for batches that were sold and batches that were not sold, right?

A. Correct.

Q. And so in the patent, someone was comfortable averaging together batches that were sold and batches that weren't sold, right?

A. Again, I don't know how comfortable that person was, but that's the end result of it.

Tr. 763:19-764:4 (Klibanov)

Ms. Los: No Distinction Between Sold and Unsold

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. All right. The 45-liter batches in this chart, Ms. Los, were any of those commercial batches?

A. I don't know the nature of those batches.

Q. Did it matter, for the purposes of your comparison, whether they were commercial batches?

A. No. At that time, it did not.

Q. Why not –

A. That wasn't one of our considerations.

Q. Why not?

A. We were working with the stability data that we were provided from regulatory, and we didn't discriminate between them.

Q. Do you think that the batches that you used are representative of what the values would be for commercial batches?

A. Yes, I do. I have no reason to think they wouldn't be.

JTX-4289.23-24 (Los Tr. 124:25-125:15, 125:17-18)

Pacira Relies on Jiangsu Hengrui's Unapproved and Unsold Batch for Infringement

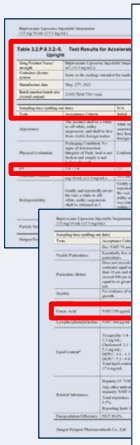


Table 3.2.P.8.3.2–3. Test Results for Accelerated Stability Study (Batch 210425BM) at 25°C ± 2°C/60% RH ± 5% RH, Upright

Drug Product Name/ strength	Bupivacaine Liposome Injectable Suspension (strength: *133 mg/10 mL (13.3 mg/mL)*)	Protocol No.	DP-P08-Y04-17026 03
Container closure system	Same as the package intended for marketing	Start time	Apr. 26th, 2021
Manufacture date	Apr. 25th, 2021	Storage condition	25°C ± 2°C/60%RH±5% RH
Batch number/batch size (Actual output)	210425BM/6808 vials	Placement method	Upright

Sampling time (pulling out date)		N/A	May. 27th, 2021	Jun. 29th, 2021	Jul. 28th,2021	Oct. 26th,2021
Tests	Acceptance Criteria	Initial	1M	2M	3M	6M
			* * *			
Erucic Acid	NMT 250 μg/mL.	ND	<64 μg/mL (23 μg/mL)[5]	<64 μg/mL (46 μg/mL)	<64 μg/mL (63 μg/mL)	88 μg/mL

JTX-4029.50-51

5: 64 μg/mL is the LOQ of erucic acid;

All Batches Tested from Swindon Meet Claim 7

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	mo.		
1	037188	45L	Skid 300 at Patheon	4/13/2017	25	ND	23	35	46	90	.7	N	JTX-4049.0037
2	037189	45L	Skid 300 at Patheon	4/19/2017	25	ND	25	35	46	89	.8	N	JTX-4049.0038
3	037190	45L	Skid 300 at Patheon	4/21/2017	25	ND	LT20	33	45	83	.8	N	JTX-4049.0039
4	037191	45L	Skid 400 at Patheon	5/9/2017	25	ND	ND	35	44	80	.9	N	JTX-4049.0040
5	037192	45L	Skid 400 at Patheon	5/11/2017	25	ND	ND	35	43	80	.9	N	JTX-4049.0041
6	037193	45L	Skid 400 at Patheon	5/15/2017	25	ND	ND	35	42	78	.9	N	JTX-4049.0042
7	047903	45L	Skid 300 and 400 at Patheon	5/17/2017	25	ND	25	34	43	79	.8	N	JTX-4049.0043 DTX-2512.20
8	126837	45L	Skid 300 at Patheon	12/14/2016	25	ND	LT20	35	41	102	.6	N	JTX-4049.0036 DTX-2519.1

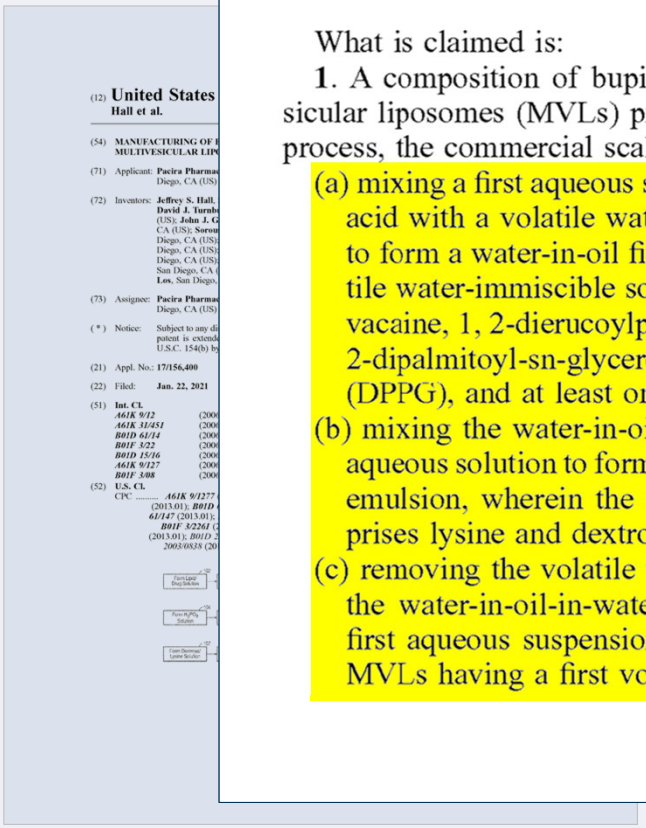
DTX-3110.1 ; *see* DTX-2465.5, 7, 9, 11, 13, 15, 17, 19

Claim Construction of "Commercial Scale"

Disputed Term	Adopted Construction
"commercial scale" '495 patent, claims 1-22	"a scale of manufacturing for production of a commercial product"
"prepared by a commercial scale process" '495 patent, claims 1-22	"prepared by a commercial scale process" is a not a product-by-process limitation

D.I. 187 at 17, 20

’495 Patent, Claim 1


(12) **United States**
Hall et al.

(54) MANUFACTURING OF … MULTIVESICULAR LIP…

(71) Applicant: **Pacira Pharma…** Diego, CA (US)

(72) Inventors: **Jeffrey S. Hall**, **David J. Turnb…** (US); **John J. G…** CA (US); **Soroush…** Diego, CA (US); Diego, CA (US); Diego, CA (US); San Diego, CA …; **Los**, San Diego,

(73) Assignee: **Pacira Pharma…** Diego, CA (US)

(*) Notice: Subject to any di… patent is extend… U.S.C. 154(b) by…

(21) Appl. No.: **17/156,400**

(22) Filed: **Jan. 22, 2021**

(51) **Int. Cl.**
A61K 9/12 (200…
A61K 31/451 (200…
B01D 61/14 (200…
B01F 3/22 (200…
B01D 15/16 (200…
A61K 9/127 (200…
B01F 3/08 (200…

(52) **U.S. Cl.**
CPC ..... ***A61K 9/1277*** (2013.01); ***B01D …*** ***61/147*** (2013.01); ***B01F 3/2261*** (2013.01); ***B01D …*** ***2003/0838*** (20…

What is claimed is:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:

(a) mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;

(b) mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;

(c) removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;

(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;

(e) exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and

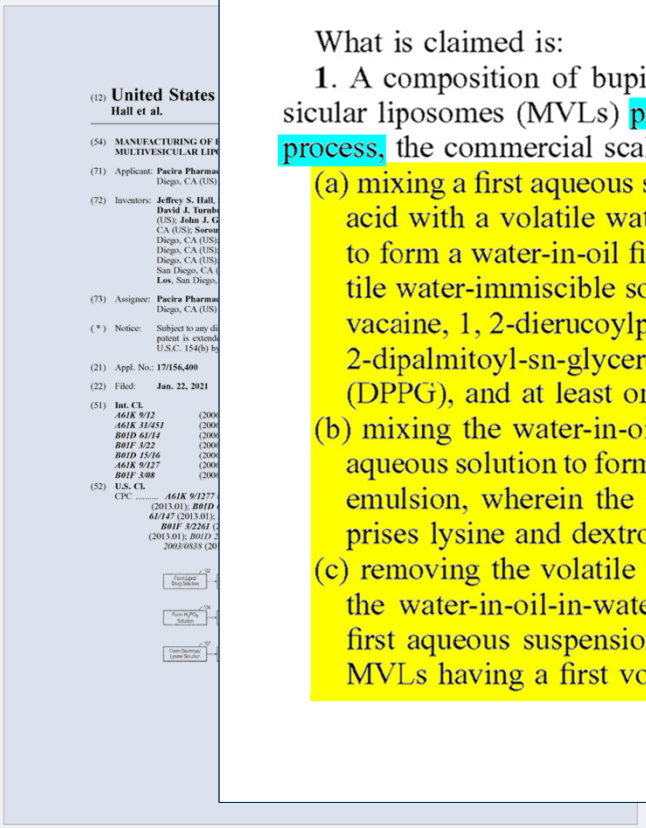
(f) further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;

wherein all steps are carried out under aseptic conditions; and

wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month.

JTX-4121.20-21, claim 1

’495 Patent, Claim 1


(12) United States
Hall et al.

(54) MANUFACTURING OF
MULTIVESICULAR LIP

(71) Applicant: Pacira Pharma
Diego, CA (US)

(72) Inventors: Jeffrey S. Hall,
David J. Turnb
(US); John J. G
CA (US); Sorou
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Diego, CA (US)
Diego, CA (US)
San Diego, CA
Los, San Diego,

(73) Assignee: Pacira Pharma
Diego, CA (US)

(*) Notice: Subject to any di
patent is extend
U.S.C. 154(b) b

(21) Appl. No.: 17/156,400

(22) Filed: Jan. 22, 2021

(51) Int. Cl.
A61K 9/12 (200
A61K 31/451 (200
B01D 61/14 (200
B01F 3/22 (200
B01D 15/16 (200
A61K 9/127 (200
B01F 3/08 (200

(52) U.S. Cl.
CPC A61K 9/1277
(2013.01); B01D
61/147 (2013.01);
B01F 3/2261 (
(2013.01); B01D 2
2003/0838 (20

What is claimed is:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:

(a) mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;

(b) mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;

(c) removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;

(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;

(e) exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and

(f) further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;

wherein all steps are carried out under aseptic conditions; and

wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month.

JTX-4121.20-21, claim 1

Amgen v. Hoffman-La Roche Applies Only to Product-by-Process Limitations

"To prove invalidity, Roche had to show that recombinant EPO was the same as urinary EPO, even though urinary EPO was not made recombinantly. The court concluded that Roche did not meet its burden because urinary EPO and recombinant EPO were structurally and functionally different. Those structural and functional differences are not explicitly part of the claim, yet are relevant as evidence of no anticipation because of the source limitation."

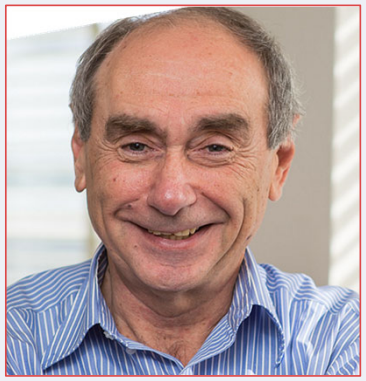
Amgen Inc. v. F. Hoffman–La Roche Ltd., 580 F.3d 1340, 1370 (Fed. Cir. 2009)

Amgen v. Hoffman-La Roche Requires Evidence of Structural and Functional Differences

"Amgen points out that, at trial, expert testimony, experimental data, and publications demonstrated differences in structure and functions between urinary EPO and recombinant EPO."

Amgen, 580 F.3d at 1366

Dr. Klibanov: No Evidence of "Structural or Functional" Differences



Dr. Alexander Klibanov

Q. You didn't do any investigation of whether there were improved structural or functional features when you compared batches made at 45 liters with batches made at 200 liters, right?

A. No, because I didn't need to.

Q. Right. You just relied on what the Court wrote in the claim construction decision and what was said in the prosecution history, right?

A. And what the patent specification says.

Q. Right. So you relied on the patent, the prosecution history, and the Court's opinion, right?

A. That's correct.

Tr. 786:5-16 (Klibanov)

Obviousness

Sold Batches of 45-L EXPAREL

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C)
of 45 L Commercial Exparel before 1/22/21

Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
					0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049.0025
14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049.0026
14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049.0027
14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	41	53	118	6.4	Y	JTX-4049.0028
16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049.0033
16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049.0032
16-3090	45L	Suite C (Skid 200)	6/9/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049.0034
18-P003	45L	Suite C (Skid 100 and 200)	6/4/2020	25	LT20	29	42	59	116	6.5	Y	JTX-4049.0051 DTX-2512.23
18-P004	45L	Suite C (Skid 100 and 200)	6/5/2020	25	LT20	28	40	56	111	6.5	Y	JTX-4049.0052 DTX-2512.23
18-P063	45L	Suite C (Skid 100)	11/29/2020	25	LT20	28	48	62	127	6.5	Y	JTX-4049.0053

1-Month Range: LT20–29 µg/mL

6-Month Range: 110–127 µg/mL

DTX-3111.1

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DTX-3111.1

Obvious When Range Is Close or Overlaps

"In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness…. We have also held that a *prima facie* case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties."

In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003)

"Because the difference between 1:7.1 and 1:10 is so slight, [prior art reference] creates a *prima facie* case of obviousness with regard to claim 6…. [Plaintiff] can rebut the *prima facie* case if it can show that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results over the prior art range."

Ortho-McNeil Pharm., Inc. v. Teva Pharm. Industries, Ltd., 344 F. App'x 595, 600 (Fed. Cir. 2009)

Dr. Schwendeman: Claimed Range and Prior Art Have "Same Properties"

Dr. Anna Schwendeman

Q. And let's look then at the six-month result. What's the range in the sold batches for the erucic acid after six months of storage at 25 degrees C in the sold batches?

A. It goes from 110 to 127.

Q. Does that overlap with the claimed range of 99 and below?

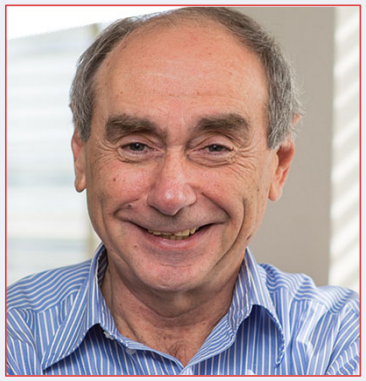
A. For sold batches, it doesn't overlap but it's very close to 90 – to about 99, so...

Q. Would a person of ordinary skill in the art expect that batches after six months of storage at 25 degrees C with 99 micrograms per milliliter of erucic acid would have the same or similar properties as ones with 110 to 115 micrograms per milliliter?

A. Yes, I expect them to be – have the same properties.

Tr. 453:17-454:4 (Schwendeman)

Dr. Klibanov: Did Not Consider If Claimed Range and Prior Art Had A "Meaningful Difference"



Dr. Alexander Klibanov

Q. And so the difference between a prior art batch at six months and the claims is 11 micrograms per milliliter, right?

A. That's correct.

Q. And you don't know whether 11 micrograms per milliliter is a meaningful difference or not, right?

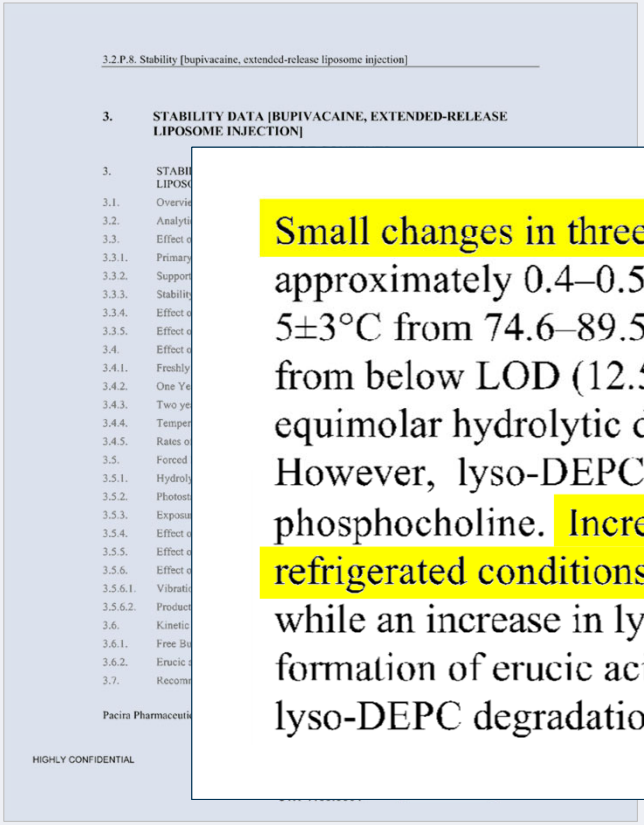
A. I have not specifically considered that issue. I think it would be, but again, I have not specifically considered that issue.

Q. Oh, now you think it would be meaningful?

A. It certainly may be meaningful, yes, but I haven't considered it.

Tr. 793:1-12 (Klibanov)

Pacira Described This Difference as "Small"


3.2.P.8. Stability [bupivacaine, extended-release liposome injection]

3. STABILITY DATA [BUPIVACAINE, EXTENDED-RELEASE LIPOSOME INJECTION]

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Small changes in three product attributes were noted. There was a small decrease in pH by approximately 0.4–0.5 units, the erucic acid concentration increased steadily over 18 months at 5±3°C from 74.6–89.5 µg/mL to 118.2–130.3 µg/mL, and lyso-DEPC also steadily increased from below LOD (12.5 µg/mL) to 46.2 – 53.8 µg/mL. Both lyso-DEPC and erucic acid are the equimolar hydrolytic degradation products of DEPC, a major lipid component of SKY0402. However, lyso-DEPC may further undergo hydrolysis to form erucic acid and glycero-3-phosphocholine. Increases in erucic acid by 30–45 µg/mL after 18 months of storage at refrigerated conditions in stability studies corresponds to about 1.0-1.5% of DEPC hydrolysis, while an increase in lyso-DEPC corresponds to 1% or less of DEPC degradation. Since the formation of erucic acid could be due to degradation of DEPC, or a combination of DEPC and lyso-DEPC degradation, erucic acid is the best indicator of the degree of DEPC hydrolysis.

JTX 4159.8

Dr. Schwendeman: "No Difference" in Shelf-life

Dr. Anna Schwendeman

Q. First, is there any difference in the shelf life for the Exparel product made at 45 liters and 200 liters?

A. No difference, is two years.

Q. And as you understand it, Dr. Schwendeman, are doctors or patients told which batch – which process is used when they get a batch?

A. They don't. When I buy vials at the University of Michigan hospital pharmacy for my research, I do not know if it's 45-liter or 200-liter.

Tr. 454:6-14 (Schwendeman)

Dr. Schwendeman: 6 Months at 25 °C Is Irrelevant

Dr. Anna Schwendeman

Q. Can you just read the second paragraph into the record?

A. Yeah. "Data presented in the NDA 22-496 in the Section 3.2.P.8.3 demonstrated the two key product attributes: Percent of free bupivacaine and erucic acid are important from the thermal stability perspective with erucic acid being shelf life limiting. Both attributes follow Arrhenius correlation, and three-month data at 25 degrees for erucic acid would be predictive of overall product stability over two years at refrigeration."

Q. Can you explain what that means?

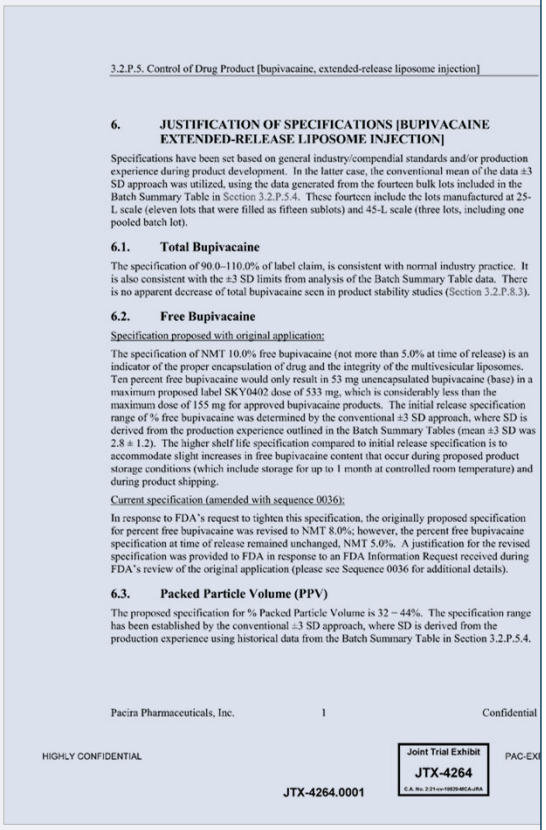
A. Meaning that whatever the data for erucic acid would be up to three months' storage of the accelerated 25 degree would be predictive of two-month – two-year stability in refrigeration. Very similar.

Q. What does that mean for six-month data at 25 degrees C? Does that correlate with the actual shelf life of the product?

A. Six months' data usually has much more erucic acid. It does not correlate with the shelf life.

Tr. 455:7-25 (Schwendeman)

No Difference in Product Performance



3.2.P.5. Control of Drug Product [bupivacaine, extended-release liposome injection]

6. JUSTIFICATION OF SPECIFICATIONS [BUPIVACAINE EXTENDED-RELEASE LIPOSOME INJECTION]

Specifications have been set based on general industry/compendial standards and/or production experience during product development. In the latter case, the conventional mean of the data ±3 SD approach was utilized, using the data generated from the fourteen bulk lots included in the Batch Summary Table in Section 3.2.P.5.4. These fourteen include the lots manufactured at 25-L scale (eleven lots that were filled as fifteen sublots) and 45-L scale (three lots, including one pooled batch lot).

6.1. Total Bupivacaine

The specification of 90.0–110.0% of label claim, is consistent with normal industry practice. It is also consistent with the ±3 SD limits from analysis of the Batch Summary Table data. There is no apparent decrease of total bupivacaine seen in product stability studies (Section 3.2.P.8.3).

6.2. Free Bupivacaine

Specification proposed with original application:

The specification of NMT 10.0% free bupivacaine (not more than 5.0% at time of release) is an indicator of the proper encapsulation of drug and the integrity of the multivesicular liposomes. Ten percent free bupivacaine would only result in 53 mg unencapsulated bupivacaine (base) in a maximum proposed label SKY0402 dose of 533 mg, which is considerably less than the maximum dose of 155 mg for approved bupivacaine products. The initial release specification range of % free bupivacaine was determined by the conventional ±3 SD approach, where SD is derived from the production experience outlined in the Batch Summary Tables (mean ±3 SD was 2.8 ± 1.2). The higher shelf life specification compared to initial release specification is to accommodate slight increases in free bupivacaine content that occur during proposed product storage conditions (which include storage for up to 1 month at controlled room temperature) and during product shipping.

Current specification (amended with sequence 0036):

In response to FDA's request to tighten this specification, the originally proposed specification for percent free bupivacaine was revised to NMT 8.0%; however, the percent free bupivacaine specification at time of release remained unchanged, NMT 5.0%. A justification for the revised specification was provided to FDA in response to an FDA Information Request received during FDA's review of the original application (please see Sequence 0036 for additional details).

6.3. Packed Particle Volume (PPV)

The proposed specification for % Packed Particle Volume is 32 – 44%. The specification range has been established by the conventional ±3 SD approach, where SD is derived from the production experience using historical data from the Batch Summary Table in Section 3.2.P.5.4.

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Joint Trial Exhibit JTX-4264

JTX-4264.0001

JTX-4264.5

6.9. Erucic Acid

Erucic acid is selected as a marker for monitoring degradation of DEPC and other lipids in SKY0402. The specification of erucic acid is NMT 310 µg/mL (or 10.0% nominal DEPC content assuming hydrolysis of one acyl chain) and NMT 155 µg/mL (or 5.0% nominal DEPC) at time of release. DEPC is the major phospholipid excipient in the formulation, and is prone to hydrolysis to erucic acid and lyso-DEPC. Lyso-DEPC may further undergo hydrolysis to form erucic acid and glycero-3-phosphocholine. Therefore, monitoring of erucic acid represents a better and more robust indicator of DEPC degradation.

In stability studies (Section 3.2.P.8.3.3.2), erucic acid has been observed at levels up to approximately 310 µg/mL at the 24-month time point (10% degradation expressed as percent of nominal DEPC equivalent) in some earlier batches of SKY0402 (05-2502, 05-2503, 06-2502 and 06-2503). This level of erucic acid was observed to have no affect on the in vitro release of SKY0402. Studies performed with aged liposome dispersions containing lysolipids as products of hydrolytic decomposition of constituent phospholipids indicate that up to 15 % degradation of phospholipid to its respective fatty acid moiety and lysophospholipid does not significantly alter the bilayer permeability[1]. In addition, the PK of the SKY0402 lot 06-2503 with approximately 310 µg/mL of erucic acid was evaluated in a Phase 1 clinical study along with low erucic acid content lots (44 – 55 µg/mL) (See Section 2.7.4.1.1.1, SKY0402-C-108). All lots showed comparable pharmacokinetic profiles, demonstrating that product with erucic acid values up to 310 µg/mL will maintain product performance.

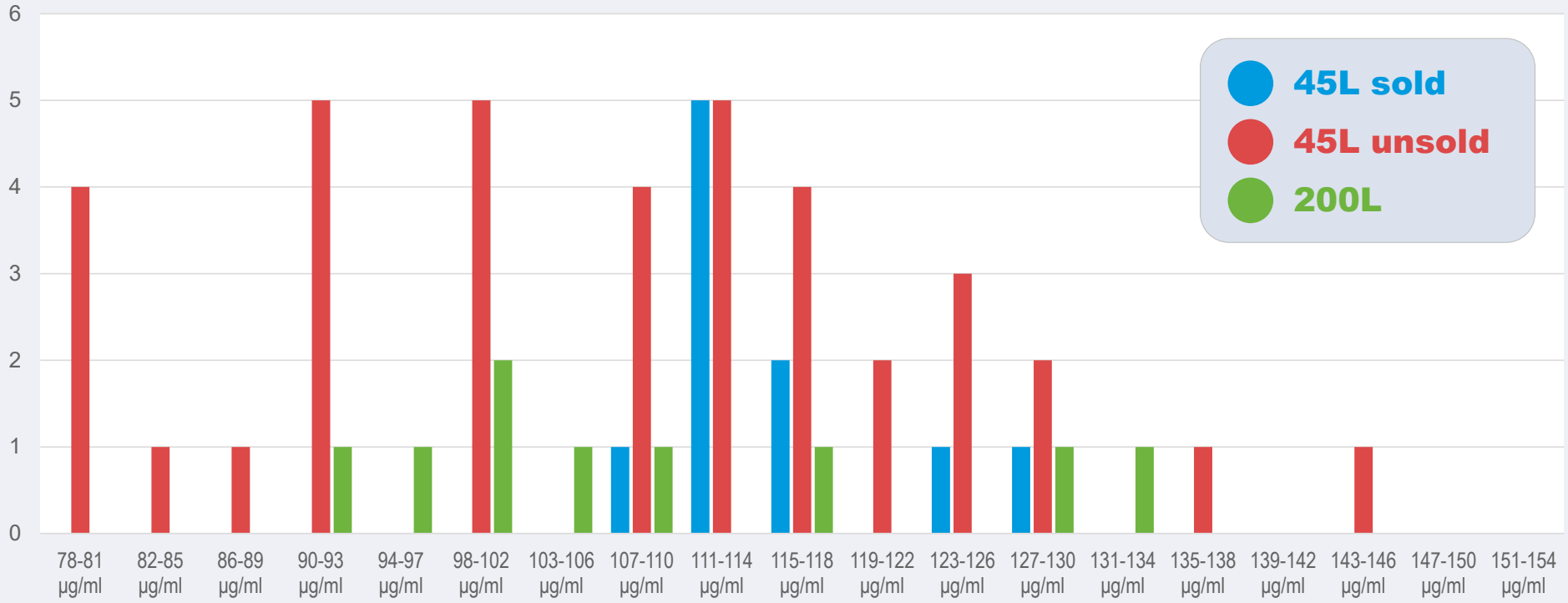
Based on this, a specification of NMT 310 µg/mL erucic acid in SKY0402 is justified. The initial release specification limit of NMT 155 µg/mL erucic acid (5% nominal DEPC degradation) is also proposed.

Small Percentages Are Differences in Degree

"Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time…. Thus, where an unexpected increase in efficacy is measured by a small percentage, as here, and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind.… Accordingly, the comparable tolerability of 0.1% and 0.3% adapalene does not indicate that the asserted claims are non-obvious."

Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 739 (Fed. Cir. 2013)

45-L and 200-L Batches – Erucic Acid Concentration after Six Months at 25 °C



DTX-3110.1-2; DTX-3114

Business-Driven Market Forces Are Not "Long-Felt Need"

"But none of [patentee's] evidence suggested that [patentee's] approach presented any technical challenge to one of ordinary skill in the art once market forces had created a demand for integrated, streaming media services…. [Patentee] may have predicted a business trend that would have proved profitable had its commercial embodiments remained competitive in the marketplace. That, however, is not a sufficient basis to overcome the strong prima facie showing of obviousness that was made in this case."

Friskit, Inc. v. Real Networks, Inc., 306 F. App'x 610, 617-18 (Fed. Cir. 2009)

Blocking Patents Undermine Long-Felt Unmet Need

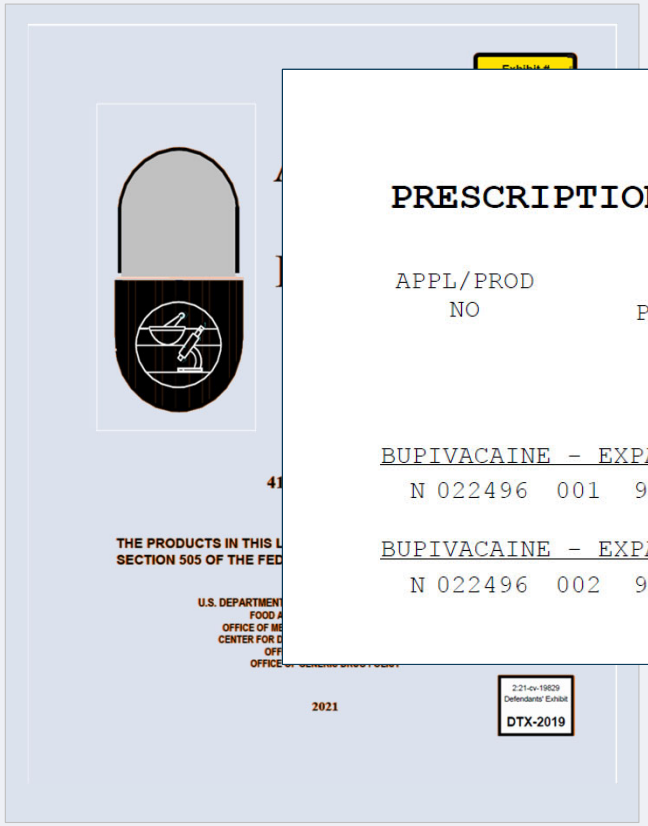
"As to long-felt but unmet need, the district court discounted its finding of such need in light of the evidence of blocking by the Elan patent. We see no clear error. While not dispositive, the evidence of blocking we have discussed is pertinent, in this case, to the factual question of long-felt but unmet need…."

Acorda Therapeutics, Inc. v. Roxane Laboratories, Inc., 903 F.3d 1310, 1342 (Fed. Cir. 2018) (internal citations omitted)

"[I]f all other variables are held constant, a blocking patent diminishes possible rewards from a non-owner's or non-licensee's investment activity aimed at an invention whose commercial exploitation would be infringing, therefore reducing incentives for innovations in the blocked space by non-owners and non-licensees of the blocking patent. Such a blocking patent therefore can be evidence that can discount the significance of evidence that nobody but the blocking patent's owners or licensees arrived at, developed, and marketed the invention covered by the later patent at issue in litigation."

Id. at 1339

The ’838 Patent Was a Blocking Patent



41ST EDITION - 2021 - APPROVED DRUG PRODUCT LIST ADA 41 of 297

PRESCRIPTION AND OTC DRUG PRODUCT PATENT AND EXCLUSIVITY LIST

APPL/PROD NO	PATENT NO	PATENT EXPIRATION DATE	PATENT CODES	PATENT DELIST REQUESTED	EXCLUSIVITY CODE(S)	EXCLUSIVITY EXPIRATION DATE
			***			
BUPIVACAINE - EXPAREL						
N 022496 001	9585838	Dec 24, 2021	DP		I-771	Apr 06, 2021
BUPIVACAINE - EXPAREL						
N 022496 002	9585838	Dec 24, 2021	DP		I-771	Apr 06, 2021

DTX-2019.1262

Non-Enablement

Asserted Claim 7 of the '495 Patent

What is claimed is:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:

(a) mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;

(b) mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;

(c) removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;

(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;

(e) exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and

(f) further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;

wherein all steps are carried out under aseptic conditions; and

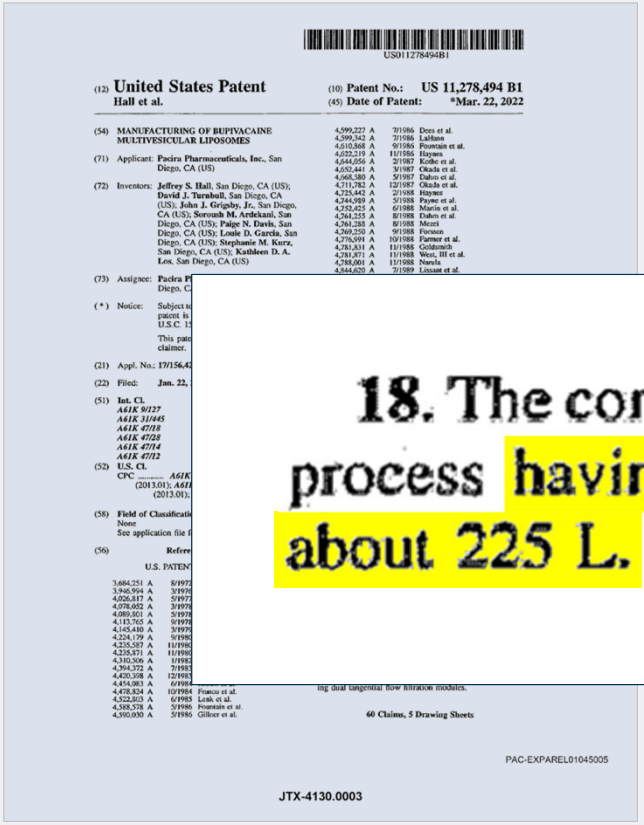
wherein the erucic acid concentration in the composition is about 23 μg/mL or less after the composition is stored at 25° C. for one month.

* * *

7. The composition of claim **1**, wherein the erucic acid concentration in the composition is about 99 μg/mL or less after the composition is stored at 25° C. for six months.

JTX-4121.20-21, claims 1, 7

Pacira Knew How to Claim a 200-L Process



US011278494B1

(12) **United States Patent**
Hall et al.

(10) **Patent No.: US 11,278,494 B1**
(45) **Date of Patent: *Mar. 22, 2022**

(54) **MANUFACTURING OF BUPIVACAINE MULTIVESICULAR LIPOSOMES**

(71) Applicant: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(72) Inventors: **Jeffrey S. Hall**, San Diego, CA (US); **David J. Turnbull**, San Diego, CA (US); **John J. Grigsby, Jr.**, San Diego, CA (US); **Soroush M. Ardekani**, San Diego, CA (US); **Paige N. Davis**, San Diego, CA (US); **Louie D. Garcia**, San Diego, CA (US); **Stephanie M. Kurz**, San Diego, CA (US); **Kathleen D. A. Los**, San Diego, CA (US)

(73) Assignee: **Pacira P** Diego, C

(*) Notice: Subject to patent is U.S.C. 15 This pate claimer.

(21) Appl. No.: **17/156,4**

(22) Filed: **Jan. 22,**

(51) **Int. Cl.**
A61K 9/127
A61K 31/445
A61K 47/18
A61K 47/28
A61K 47/14
A61K 47/12

(52) **U.S. Cl.**
CPC *A61K* (2013.01); *A61* (2013.01);

(58) **Field of Classificati**
None
See application file f

(56) **Refere**

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ing dual tangential flow filtration modules.

60 Claims, 5 Drawing Sheets

PAC-EXPAREL01045005

JTX-4130.0003

18. The composition of claim 1, prepared by a commercial process having a final product volume of about 200 L to about 225 L.

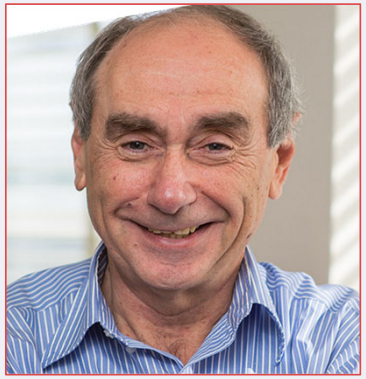
JTX-4130.23 ('494 Patent), claim 18

Manufacturing MVLs Is "Very Complex"

"[T]he manufacturing process required to form the MVLs that comprise EXPAREL® is very complex and involves multiple emulsion steps that must be performed under precisely controlled conditions."

Tr. 584:25-585:17 (Yaman) (reading Pacira's interrogatory response)

Scaling Up MVLs Is Complex and Unpredictable



Dr. Alexander Klibanov

Q. Dr. Klibanov, scaling up is far from straightforward in your view, right?

A: That's correct.

Q: It's not nearly as simple as just using more raw materials and bigger equipment?

A: That's right.

Q: Because processes often behave differently at different scales, right?

A: That's correct as well.

Tr. 802:16-26 (Klibanov)

Dr. Grisby (Named Inventor): Pacira Still Unable to Practice Its Own Claims

Dr. John Grigsby

PACIRA PHARMACEUTICALS, INC.

Q. Since then, has Pacira made more batches using the 200-liter process?

A. Yes, we have.

Q. Have all of those batches had an erucic acid level of 99 micrograms or less at six months under accelerated conditions?

A. Well, not every batch is tested at accelerated conditions, but we did make additional ones, some did, some did not.

Q. Do you want every batch to have a 99 micrograms or less of erucic acid at six months under accelerated conditions?

A. Yes, we do.

Tr. 178:24-179:9 (Grigsby)

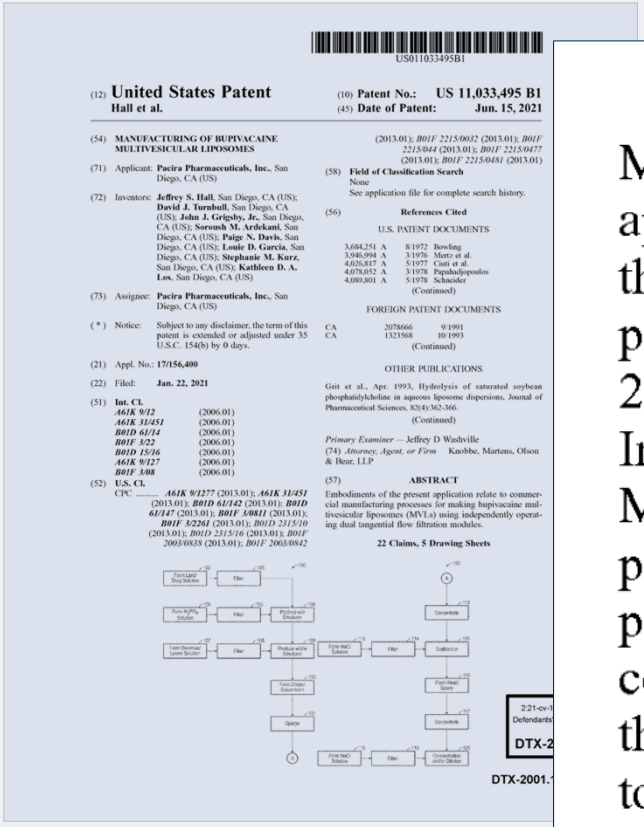
Pacira's 200-L Batches Do Not Meet Claim 7

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 200 L Exparel

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.	
1	129855	200L	Suite SWC2B (Skid 500) in Swindon	3/16/2020	25	ND	22	36	54	99	6.5	JTX-4075.0001 DTX-2374.1 DTX-2535.3
2	129856	200L	Suite SWC2B (Skid 500) in Swindon	3/23/2020	25	ND	23	38	51	96	6.5	JTX-4075.0002 DTX-2368.1 DTX-2535.3
3	129860	200L	Suite SWC2B (Skid 500) in Swindon	3/31/2020	25	ND	23	38	54	98	6.5	JTX-4075.0003 DTX-2346.1 DTX-2535.3
4	120862	200L	Suite SWC2B (Skid 500) in Swindon	1/29/2021	25	ND	LT20	33	45	92	6.4	DTX-2336.19 DTX-2373.1 DTX-2531.8
5	120863 ✗	200L	Suite SWC2B (Skid 500) in Swindon	2/1/2021	25	23	34 ✗	42	60	115 ✗	6.4	DTX-2336.21 DTX-2360.1 DTX-2531.2
6	120864 ✗	200L	Suite SWC2B (Skid 500) in Swindon	2/4/2021	25	LT20	28 ✗	37	51	108 ✗	6.4	DTX-2336.23 DTX-2367.1 DTX-2531.2
7	21-2001 ✗	200L	Suite SWC2B (Skid 500) in Swindon	7/26/2021	25	27	37 ✗	53	71	133 ✗	6.2	DTX-2551.1 JTX-4125.0001 DTX-2533.2
8	21-2002 ✗	200L	Suite SWC2B (Skid 500) in Swindon	7/29/2021	25	28	35 ✗	51	68	128 ✗	6.2	DTX-2552.1 DTX-2344.1 DTX-2336.26 DTX-2533.2
9	21-2003 ✗	200L	Suite SWC2B (Skid 500) in Swindon	7/27/2021	25	LT20	26 ✗	37	52	106 ✗	6.3	DTX-2553.1 JTX-4256.0001 DTX-2336.25 DTX-2533.2

DTX-3114

Pacira's Lysine and Internal pH Theory



US011033495B1

(12) **United States Patent**
Hall et al.

(10) **Patent No.: US 11,033,495 B1**
(45) **Date of Patent: Jun. 15, 2021**

(54) **MANUFACTURING OF BUPIVACAINE MULTIVESICULAR LIPOSOMES**

(71) Applicant: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(72) Inventors: **Jeffrey S. Hall**, San Diego, CA (US); **David J. Turnbull**, San Diego, CA (US); **John J. Grigsby, Jr.**, San Diego, CA (US); **Soroush M. Ardekani**, San Diego, CA (US); **Paige N. Davis**, San Diego, CA (US); **Louie D. Garcia**, San Diego, CA (US); **Stephanie M. Kurz**, San Diego, CA (US); **Kathleen D. A. Los**, San Diego, CA (US)

(73) Assignee: **Pacira Pharmaceuticals, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/156,400**

(22) Filed: **Jan. 22, 2021**

(51) **Int. Cl.**
A61K 9/12 (2006.01)
A61K 31/451 (2006.01)
B01D 61/14 (2006.01)
B01F 3/22 (2006.01)
B01D 15/16 (2006.01)
A61K 9/127 (2006.01)
B01F 3/08 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 9/1277*** (2013.01); ***A61K 31/451*** (2013.01); ***B01D 61/142*** (2013.01); ***B01D 61/147*** (2013.01); ***B01F 3/0811*** (2013.01); ***B01F 3/2261*** (2013.01); ***B01D 2315/10*** (2013.01); ***B01D 2315/16*** (2013.01); ***B01F 2003/0838*** (2013.01); ***B01F 2003/0842*** (2013.01); ***B01F 2215/0032*** (2013.01); ***B01F 2215/044*** (2013.01); ***B01F 2215/0477*** (2013.01); ***B01F 2215/0481*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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(Continued)

Primary Examiner — Jeffrey D Washville
(74) *Attorney, Agent, or Firm* Knobbe, Martens, Olson & Bear, LLP

(57) **ABSTRACT**

Embodiments of the present application relate to commercial manufacturing processes for making bupivacaine multivesicular liposomes (MVLs) using independently operating dual tangential flow filtration modules.

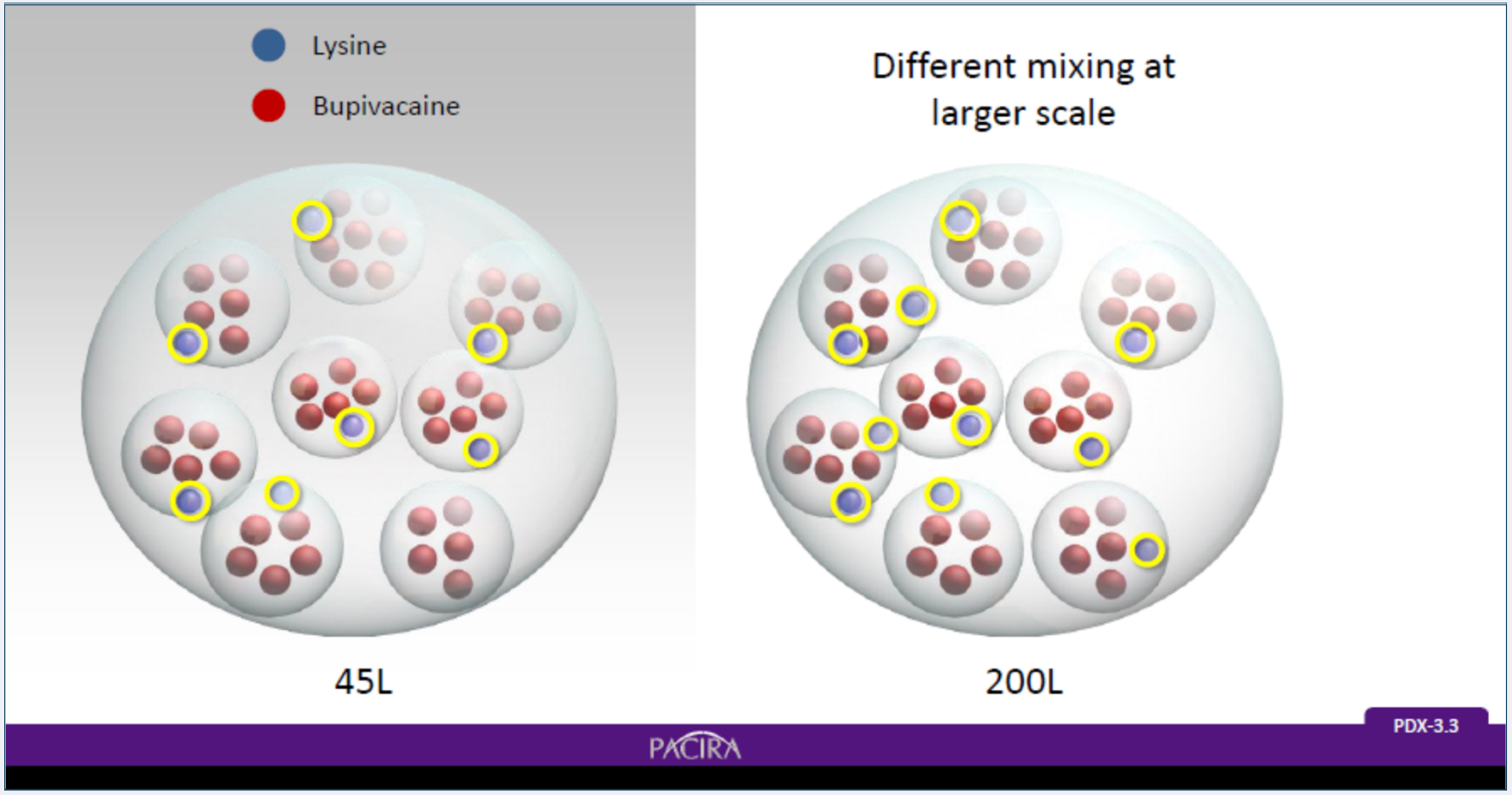
22 Claims, 5 Drawing Sheets

DTX-2001.1

JTX-4121.20

It was observed that the total suspensions and bupivacaine MVL particles prepared by the present process contained approximately 17% and 13% more dextrose, respectively, than those samples prepared by the existing commercial process. In addition, the lysine concentration was 8% and 29% more in those samples prepared by the present process. In addition, the internal and external pH of the bupivacaine MVL compositions were also measured. The higher internal pH of the bupivacaine MVL particles prepared by the present process may be attributable to the higher lysine concentration inside the MVL particles. As discussed above, the slight increase in MVL internal pH may also contribute to the stability of the lipid membranes.

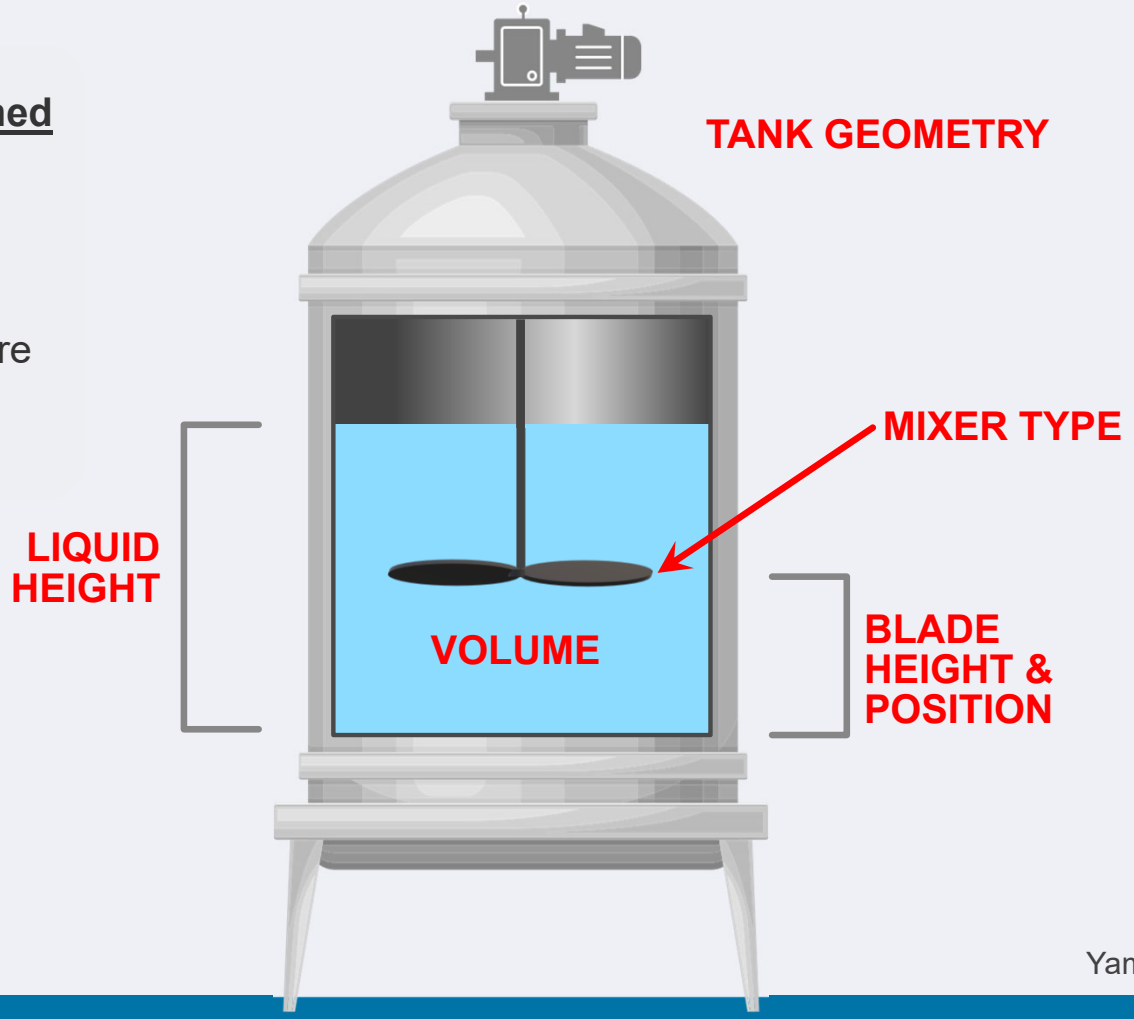
Pacira's "Explanation" for Improved Stability



Exemplary Undisclosed Emulsion Mixing Parameters

Parameters Mentioned

- Blade diameter
- Mixing speed
- Mixing temperature
- Mixing time



Yaman Demonstrative, DTX-3.11

Mr. Hall (Named Inventor): Undisclosed Parameters Will Impact Mixing Performance

Gregory Hall

PACIRA PHARMACEUTICALS, INC.

Tr. 121:7-9, 21-23
122:6-12 (Hall)

Q: Okay. The type of mixer that's used will impact the mixing performance, correct?

A: That is true.

* * *

Q: And the mixing parameters will impact the size of those liposome particles, right?

A: They will.

* * *

Q: [F]or the emulsion steps, a different blade diameter could potentially require a different mixing time speed?

A: That's right.

Q: And so the vessel geometry will also impact the mixing performance, right?

A: Likely, yes.

Pacira's Experimentation

3.2.P.2. Pharmaceutical Development [bupivacaine, liposome injectable suspension] Swindon 200L

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Table 1: Comparison of Vessels for the Suite SWC2 (45 L) and Suite SWC2B (200 L) Process Skids

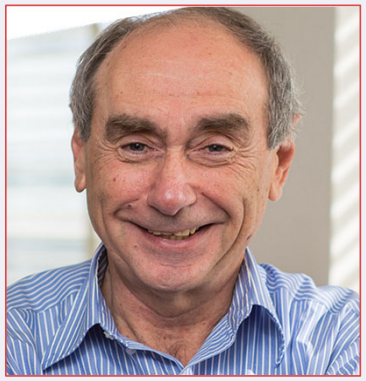
Vessel	Suite SWC2 (45 L)	Suite SWC2B (200 L)
	* * *	
Emulsification Vessel (both first and second emulsion)	**V11** Capacity: 200 L Internal Diameter: 24" Shell Wall Height: 26" Jacketed, 2 Baffles, Vortex Breaker Scott Turbine High Shear Mixer Single 7" Cowles blade	**V11** Capacity: 1000 L Internal Diameter: 42" Shell Wall Height: 45" Jacketed, 2 Baffles, 2 Vortex Breaker 2 Scott Turbine High Shear Mixers 11" and 14" Cowles blades

JTX-4188.7, 23

Table 11: Summary of Processing Parameters for 200 L Skid 500

Unit Operation	Parameter		200 L Registration Set Points	200 L Established Process Ranges
First Emulsification	Mixing Speed (rpm)		1150	1100 – 1200
	Mixing Time (min)		70	69 – 71
	Temperature (°C)		21.5	20.5 – 22.5
Second Emulsification	Mixing Speed (rpm)		450	470[1] – 510
	Mixing Time (sec)		60	55 – 65
	Temperature (°C)		21.5	21.5
Sparge	Total Flow Rate (L/min)		2442	2321 – 2566
	Sparge Ring 1 (L/min)		650	618 – 683
	Sparge Ring 2 (L/min)		932	885 – 979
	Sparge Ring 3 (L/min)		430	409 – 452
	Sparge Ring 4 (L/min)		430	409 – 452
	Time (min)		25	24 – 26
	Temperature (°C)		22.0	20.5 – 22.5
Initial Concentration	Retentate Flow Rate (L/min)		150	140 – 170
	Permeate Flow Rate (L/min)		32	24 – 40
Diafiltration (Buffer Exchange)	Hold Volume (L)		315	300 – 330
	Buffer Volume Exchange (VE)		4	4 – 4.5
	Retentate Flow Rate (L/min)		155	140 – 170
	Permeate Flow Rate (L/min)		20	10 – 25
	Volume Exchange 0 – 3.5	Total Nitrogen Flush Flow Rate (L/min)	1000	1000 – 1400
		Flush Tube 1 (L/min)	250	250 – 350
		Flush Tube 2 (L/min)	250	250 – 350
		Flush Tube 3 (L/min)	250	250 – 350
		Flush Tube 4 (L/min)	250	250 - 350
Diafiltration (Buffer Exchange)	Volume Exchange 3.5 – 4.5	Total Nitrogen Flush Flow Rate (L/min)	1500	1500 – 2200
		Flush Tube 1 (L/min)	375	100 – 375
		Flush Tube 2 (L/min)	375	375 – 1000
		Flush Tube 3 (L/min)	375	100 – 375
		Flush Tube 4 (L/min)	375	375 – 1000

Dr. Klibanov: Substantial Experimentation Is Required



Dr. Alexander Klibanov

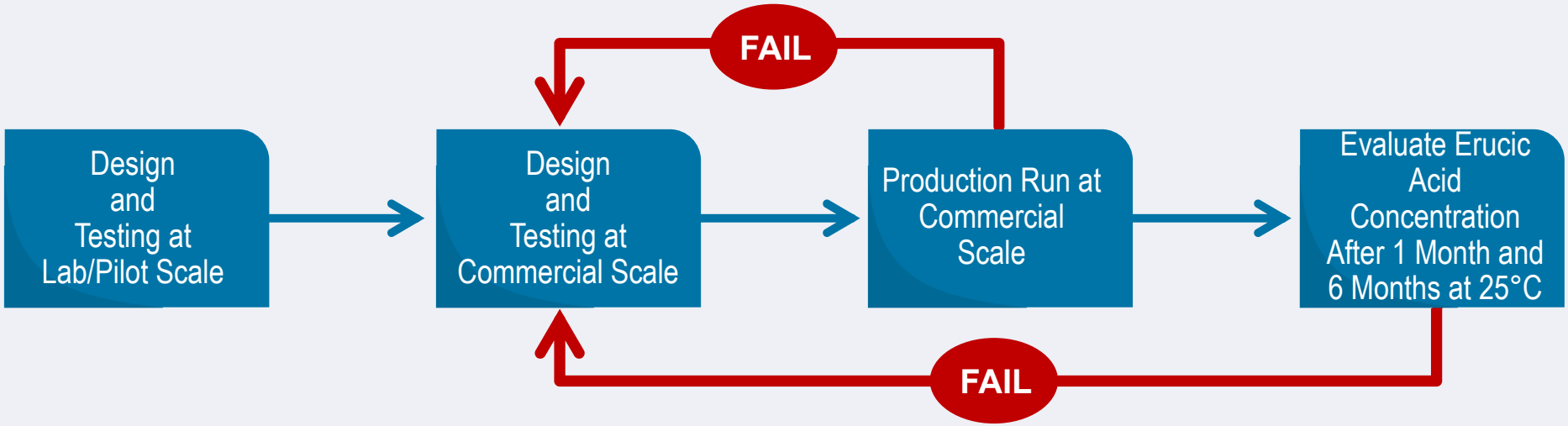
Q: Now, on this factor, how do you view the quantity of experimentation in view of the patent's disclosure?

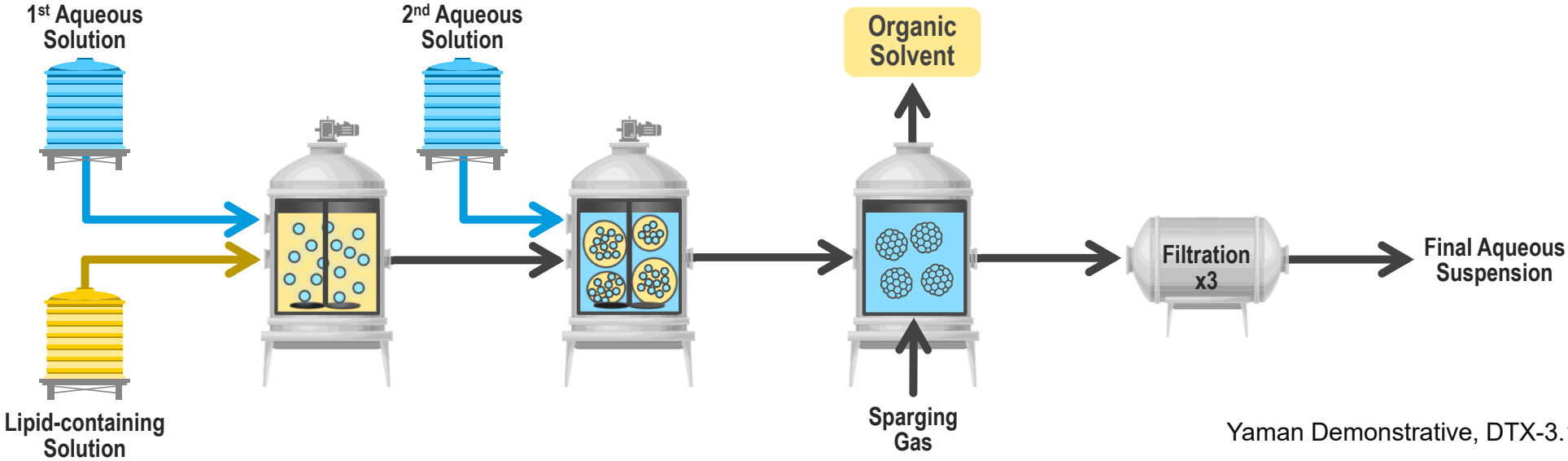
A: I view it as substantial but routine as to a person of ordinary skill in the art, as opposed to undue.

Q: And why is that?

A: Well, because a person of ordinary skill in the art, in this particular art, as I just explained repeatedly, would expect a substantial amount of experimentation, which experimentation this person would still view as routine.

Tr. 751:3-11 (Klibanov)





Yaman Demonstrative, DTX-3.13

Amgen, Inc. v. Sanofi, 598 U.S. 594 (2023)

> A "trial-and-error method for finding functional antibodies" and "requir[ing] scientists to make substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too … is not enablement. More nearly, it is 'a hunting license.'"

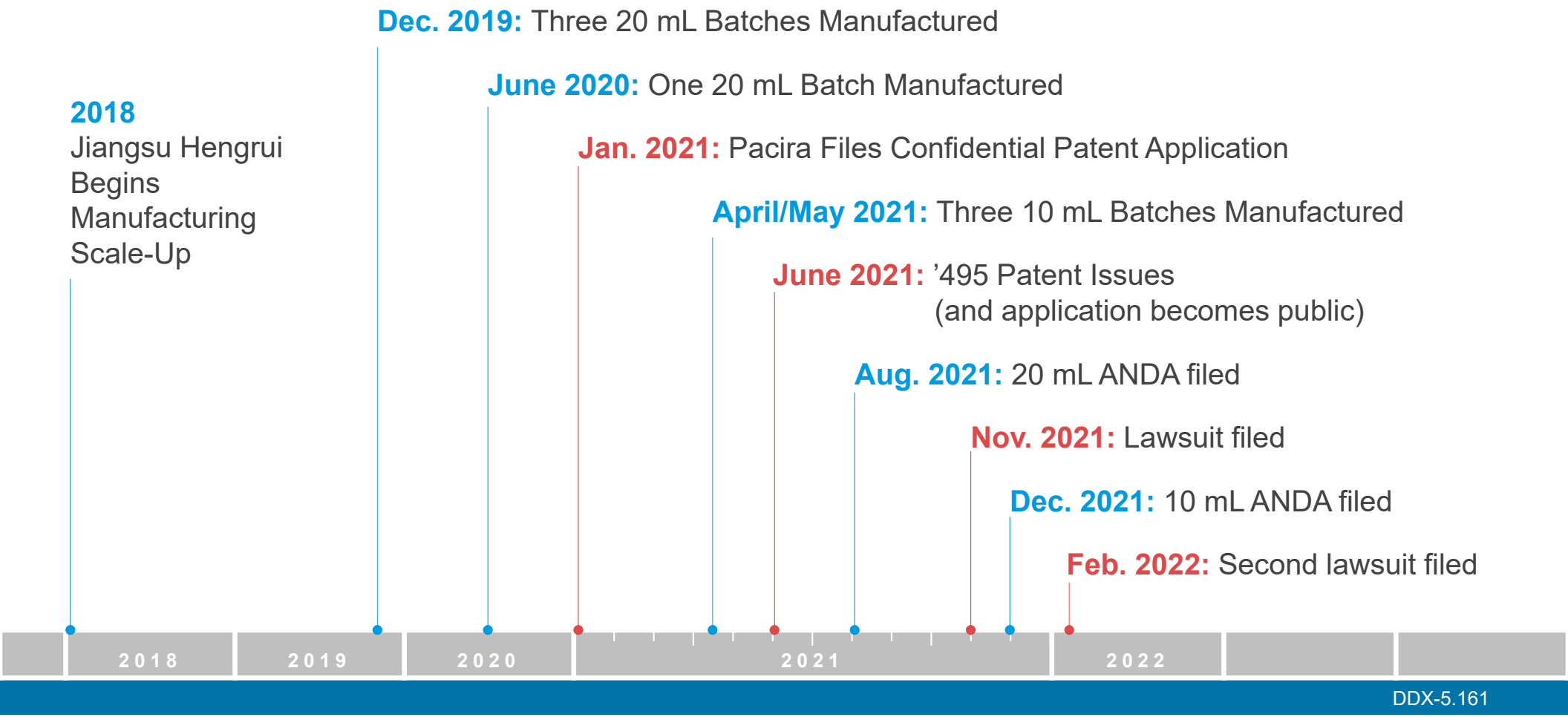
Amgen, 598 U.S. at 614

> "[T]he more a party claims, the broader the monopoly it demands, the more it must enable. That holds true whether the case involves telegraphs devised in the 19th century, glues invented in the 20th, or antibody treatments developed in the 21st."

Id. at 613.

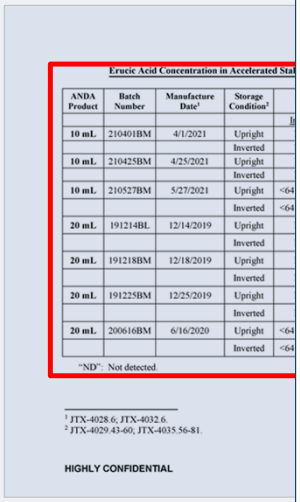
Non-Infringement

Jiangsu Hengrui's Development



DDX-5.161

No ANDA Batches Made Since 2021


Erucic Acid Concentration in Accelerated Stab

ANDA Product	Batch Number	Manufacture Date[1]	Storage Condition[2]	
				I
10 mL	210401BM	4/1/2021	Upright	
			Inverted	
10 mL	210425BM	4/25/2021	Upright	
			Inverted	
10 mL	210527BM	5/27/2021	Upright	<64
			Inverted	<64
20 mL	191214BL	12/14/2019	Upright	
			Inverted	
20 mL	191218BM	12/18/2019	Upright	
			Inverted	
20 mL	191225BM	12/25/2019	Upright	
			Inverted	
20 mL	200616BM	6/16/2020	Upright	<64
			Inverted	<64

"ND": Not detected.

[1] JTX-4028.6; JTX-4032.6.
[2] JTX-4029.43-60; JTX-4035.56-81.

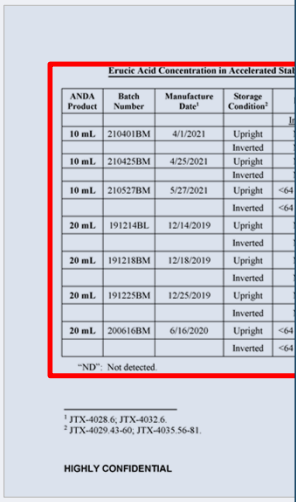
HIGHLY CONFIDENTIAL

DTX-3107

Erucic Acid Concentration in Accelerated Stability Testing (25°C) of 10 mL and 20 mL ANDA Product

ANDA Product	Batch Number	Manufacture Date[1]	Storage Condition[2]	Erucic Acid Concentration during Accelerated Stability Testing (25 °C)[2]				
				Initial	1 mo.	2 mos.	3 mos.	6 mos.
10 mL	210401BM	4/1/2021	Upright	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	101 µg/mL
			Inverted	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	96 µg/mL
10 mL	210425BM	4/25/2021	Upright	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	88 µg/mL
			Inverted	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	83 µg/mL
10 mL	210527BM	5/27/2021	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	99 µg/mL	123 µg/mL
			Inverted	<64 µg/mL	<64 µg/mL	<64 µg/mL	98 µg/mL	126 µg/mL
20 mL	191214BL	12/14/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	123 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	120 µg/mL
20 mL	191218BM	12/18/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	118 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	116 µg/mL
20 mL	191225BM	12/25/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	118 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	120 µg/mL
20 mL	200616BM	6/16/2020	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	66 µg/mL	139 µg/mL
			Inverted	<64 µg/mL	<64 µg/mL	<64 µg/mL	67 µg/mL	134 µg/mL

No ANDA Batches Met Both One- and Six-Month Limitations


Erucic Acid Concentration in Accelerated Stab

ANDA Product	Batch Number	Manufacture Date[1]	Storage Condition[2]	
10 mL	210401BM	4/1/2021	Upright	
			Inverted	
10 mL	210425BM	4/25/2021	Upright	
			Inverted	
10 mL	210527BM	5/27/2021	Upright	<64
			Inverted	<64
20 mL	191214BL	12/14/2019	Upright	
			Inverted	
20 mL	191218BM	12/18/2019	Upright	
			Inverted	
20 mL	191225BM	12/25/2019	Upright	
			Inverted	
20 mL	200616BM	6/16/2020	Upright	<64
			Inverted	<64

"ND": Not detected.

[1] JTX-4028.6; JTX-4032.6.
[2] JTX-4029.43-60; JTX-4035.56-81.

HIGHLY CONFIDENTIAL

DTX-3107

Erucic Acid Concentration in Accelerated Stability Testing (25°C) of 10 mL and 20 mL ANDA Product

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				Initial	1 mo.	2 mos.	3 mos.	6 mos.
10 mL	210401BM	4/1/2021	Upright	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	101 µg/mL
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10 mL	210425BM	4/25/2021	Upright	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	88 µg/mL
			Inverted	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	83 µg/mL
10 mL	210527BM	5/27/2021	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	99 µg/mL	123 µg/mL
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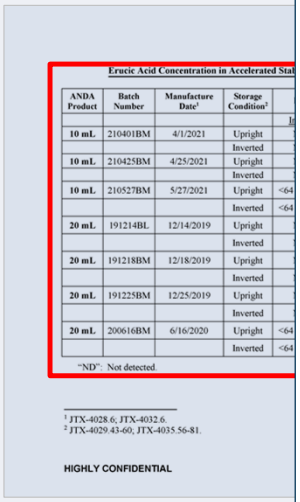
20 mL	191214BL	12/14/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	123 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	120 µg/mL
20 mL	191218BM	12/18/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	118 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	116 µg/mL
20 mL	191225BM	12/25/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	118 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	120 µg/mL
20 mL	200616BM	6/16/2020	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	66 µg/mL	139 µg/mL
			Inverted	<64 µg/mL	<64 µg/mL	<64 µg/mL	67 µg/mL	134 µg/mL

No ANDA Batches Met Claim 7


Erucic Acid Concentration in Accelerated Stab

ANDA Product	Batch Number	Manufacture Date[1]	Storage Condition[2]	
				In
10 mL	210401BM	4/1/2021	Upright	
			Inverted	
10 mL	210425BM	4/25/2021	Upright	
			Inverted	
10 mL	210527BM	5/27/2021	Upright	<64
			Inverted	<64
20 mL	191214BL	12/14/2019	Upright	
			Inverted	
20 mL	191218BM	12/18/2019	Upright	
			Inverted	
20 mL	191225BM	12/25/2019	Upright	
			Inverted	
20 mL	200616BM	6/16/2020	Upright	<64
			Inverted	<64

"ND": Not detected.

[1] JTX-4028.6; JTX-4032.6.
[2] JTX-4029.43-60; JTX-4035.56-81.

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DTX-3107

Erucic Acid Concentration in Accelerated Stability Testing (25°C) of 10 mL and 20 mL ANDA Product

ANDA Product	Batch Number	Manufacture Date[1]	Storage Condition[2]	Erucic Acid Concentration during Accelerated Stability Testing (25 °C)[2]				
				Initial	1 mo.	2 mos.	3 mos.	6 mos.
10 mL	210401BM	4/1/2021	Upright	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	101 µg/mL
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10 mL	210425BM	4/25/2021	Upright	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	88 µg/mL
			Inverted	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	83 µg/mL
10 mL	210527BM	5/27/2021	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	99 µg/mL	123 µg/mL
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20 mL	191214BL	12/14/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	123 µg/mL
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20 mL	200616BM	6/16/2020	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	66 µg/mL	139 µg/mL
			Inverted	<64 µg/mL	<64 µg/mL	<64 µg/mL	67 µg/mL	134 µg/mL

No ANDA Batches Met Both One- and Six-Month Limitations

Erucic Acid Concentration in Accelerated Stability Testing (25°C) of 10 mL and 20 mL ANDA Product

ANDA Product	Batch Number	Manufacture Date[1]	Storage Condition[2]	Erucic Acid Concentration during Accelerated Stability Testing (25 °C)[2]				
10 mL	210425BM	4/25/2021	Upright	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	88 µg/mL
			Inverted	ND	<64 µg/mL	<64 µg/mL	<64 µg/mL	83 µg/mL
10 mL	210527BM	5/27/2021	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	99 µg/mL	123 µg/mL
			Inverted	<64 µg/mL	<64 µg/mL	<64 µg/mL	98 µg/mL	126 µg/mL
20 mL	191214BL	12/14/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	123 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	120 µg/mL
20 mL	191218BM	12/18/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	118 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	116 µg/mL
20 mL	191225BM	12/25/2019	Upright	ND	ND	<64 µg/mL	<64 µg/mL	118 µg/mL
			Inverted	ND	ND	<64 µg/mL	<64 µg/mL	120 µg/mL
20 mL	200616BM	6/16/2020	Upright	<64 µg/mL	<64 µg/mL	<64 µg/mL	66 µg/mL	139 µg/mL
			Inverted	<64 µg/mL	<64 µg/mL	<64 µg/mL	67 µg/mL	134 µg/mL

"ND": Not detected.

[1] JTX-4028.6; JTX-4032.6.
[2] JTX-4029.43-60; JTX-4035.56-81.

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DTX-3107

Limit of Quantitation ("LOQ") = 64 µg/mL

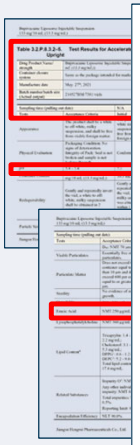


Table 3.2.P.8.3.2–3. Test Results for Accelerated Stability Study (Batch 210425BM) at 25°C ± 2°C/60% RH ± 5% RH, Upright

Drug Product Name/ strength	Bupivacaine Liposome Injectable Suspension (strength: *133 mg/10 mL (13.3 mg/mL)*)	Protocol No.	DP-P08-Y04-17026 03
Container closure system	Same as the package intended for marketing	Start time	Apr. 26th, 2021
Manufacture date	Apr. 25th, 2021	Storage condition	25°C ± 2°C/60%RH±5% RH
Batch number/batch size (Actual output)	210425BM/6808 vials	Placement method	Upright

Sampling time (pulling out date)		N/A	May. 27th, 2021	Jun. 29th, 2021	Jul. 28th,2021	Oct. 26th,2021
Tests	Acceptance Criteria	Initial	1M	2M	3M	6M
			* * *			
Erucic Acid	NMT 250 µg/mL.	ND	<64 µg/mL (23 µg/mL)[5]	<64 µg/mL (46 µg/mL)	<64 µg/mL (63 µg/mL)	88 µg/mL

JTX-4029.50-51

5: 64 µg/mL is the LOQ of erucic acid;

Dr. Karaborni: No Confidence in Values Below the LOQ

Dr. Sami Karaborni

Q. And you understand that the LOQ for Jiangsu Hengrui's assay was 64 micrograms per mL, right?

A. Yes.

Q. So any value that Jiangsu Hengrui has reported there that's lower than 64 micrograms per mL can't be determined with suitable precision or accuracy; right?

A. Yes.

Q. The number that you are pointing to here is 23, right?

A. Yes.

Q. So you don't have too much confidence in that number because it's below the LOQ, right?

A. Yes.

Tr. 294:11-22 (Karaborni)

Ms. Los: Below the LOQ, an Assay "Can't Tell You Exactly How Much"

Kathleen Los

PACIRA PHARMACEUTICALS, INC.

Q. In a general terminology sense, Ms. Los, what does the limit of quantification mean?

A. Whenever you validate an assay, you validate it across a certain range, low to high, and that means that the signal for these samples was lower than the validated lower limit for quantitation.

Q. So would it be fair to say, Ms. Los, that some erucic was detected in these samples, something less than 20, but the assay can't tell you exactly how much?

A. Yes, that's what that means.

JTX-4289.24 (Los Tr.) at 126:3-4, 126:6-14, 126:16

Dr. Schwendeman: Cannot Accurately Tell Concentration Below the LOQ

Dr. Anna Schwendeman

Q. Did you hear [Ms. Los] explain in the deposition that the limit of quantification is some – means that some erucic acid was detected in the same, something less than whatever the limit of quantification is, but the assay can't tell us exactly how much?

A. Yes. The assay cannot accurately tell the concentration below the 64 or below the limit of quantification.

Q. And do you agree that that's a correct definition of LOQ?

A. I agree with the definition of LOQ.

Tr. 396:17-25 (Schwendeman)

Dr. Cui (Jiangsu Hengrui): Cannot Determine Accuracy of Data Below the LOQ

Dr. Hongying Cui

Q. ...Does LOQ mean the lowest concentration of the substance that can be measured with certainty using standard tests?

A. Yes.

Q. So "LOQ" refers to the lowest concentration that could be measured with certainty. Is that – wouldn't you agree that the 52 micrograms/milliliter included here in the parentheses isn't the result of reliable tests?

A. Because this number is below the LOQ, and therefore, the accuracy of this data cannot be determined.

JTX-4285.12-13 (Cui Tr. 87:11-13, 87:15, 87:21-25, 88:2-4)

Sunovion Does Not Apply

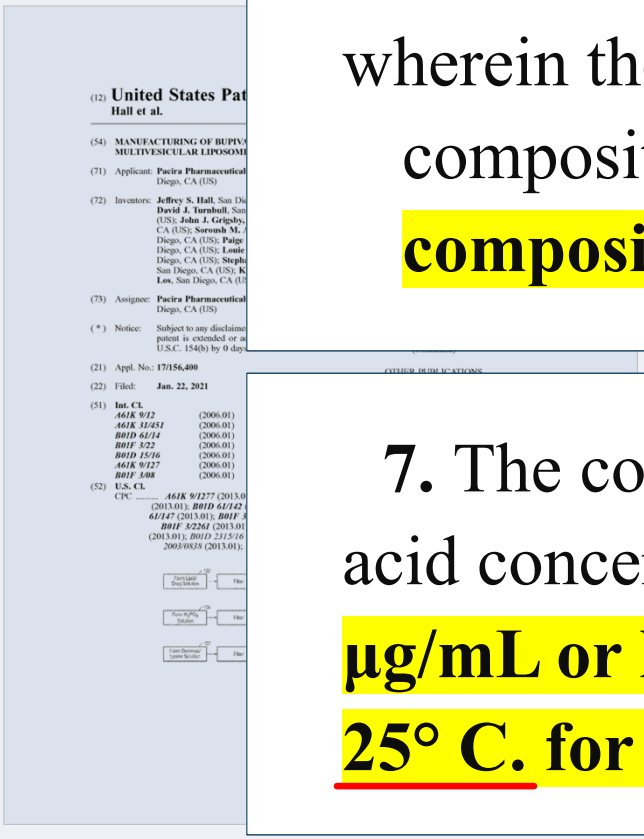
"When an ANDA is silent with respect to infringement . . . the correct analysis is under *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997), not *Sunovion*."

Ferring B.V. v. Watson Lab'ys, Inc.-Fla.,
764 F.3d 1382, 1387-88 (Fed. Cir. 2014) ("Ferring II")

"In cases in which the ANDA specification does not resolve the infringement question in the first instance, we have endorsed the district court's reference to relevant evidence, including biobatch data and actual samples of the proposed generic composition that the ANDA filer had submitted to the FDA."

Ferring B.V. v. Watson Lab'ys, Inc.-Fla.,
764 F.3d 1401, 1409 (Fed. Cir. 2014) ("Ferring I")

’495 Patent, Claim 7



wherein the erucic acid concentration in the composition is **about 23 µg/mL or less after the composition is stored at 25° C. for one month**.

7. The composition of claim 1, wherein the erucic acid concentration in the composition is **about 99 µg/mL or less after the composition is stored at 25° C. for six months**.

JTX-4121.21, claims 1, 7

ICH Decision Tree

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

EVALUATION FOR STABILITY DATA
Q1E

Current *Step 4* version
dated 6 February 2003

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

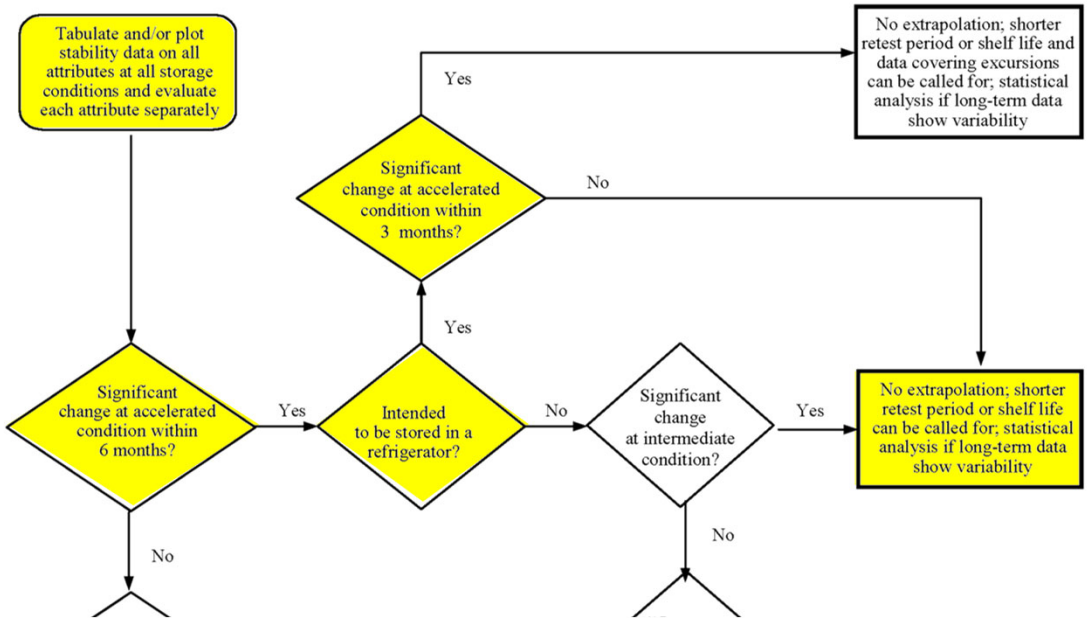
2:21-cv-19829 Defendants' Exhibit DTX-3061

Exhibit Karaborni 08 12/08/2023 - JB

PAC-EXPAREL04164619
DTX-3061.1

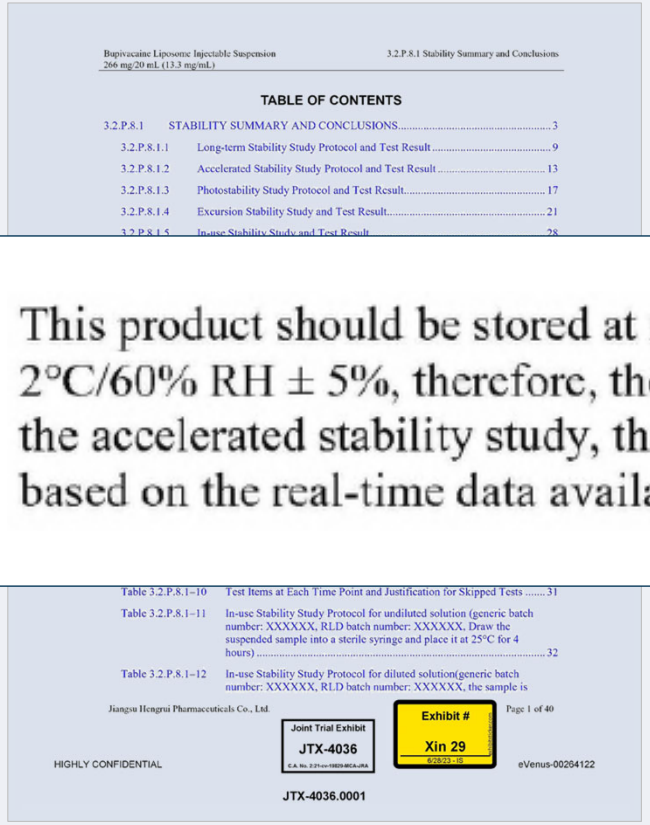
3. APPENDICES

Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding Frozen Products)



DTX-3061.12

The ANDA Products' Shelf-life Is Based on 5 °C Test Results



Bupivacaine Liposome Injectable Suspension 266 mg/20 mL (13.3 mg/mL) 3.2.P.8.1 Stability Summary and Conclusions

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Joint Trial Exhibit JTX-4036 C.A. No. 2:21-cv-19829-MCA-JRA

Exhibit # Xin 29 6/28/23 - IR

HIGHLY CONFIDENTIAL eVenus-00264122

JTX-4036.0001

This product should be stored at refrigerated at 2° to 8°C and accelerated condition is 25°C ± 2°C/60% RH ± 5%, therefore, there is no intermediate storage condition possible. Due to failure of the accelerated stability study, the proposed expiration period of the generic drug product should be based on the real-time data available at the long-term storage condition.

JTX 4036.13

Dr. Schwendeman: Shelf-life Based on 5 °C, Not 25 °C

Dr. Anna Schwendeman

Tr. 406:11-23 (Schwendeman)

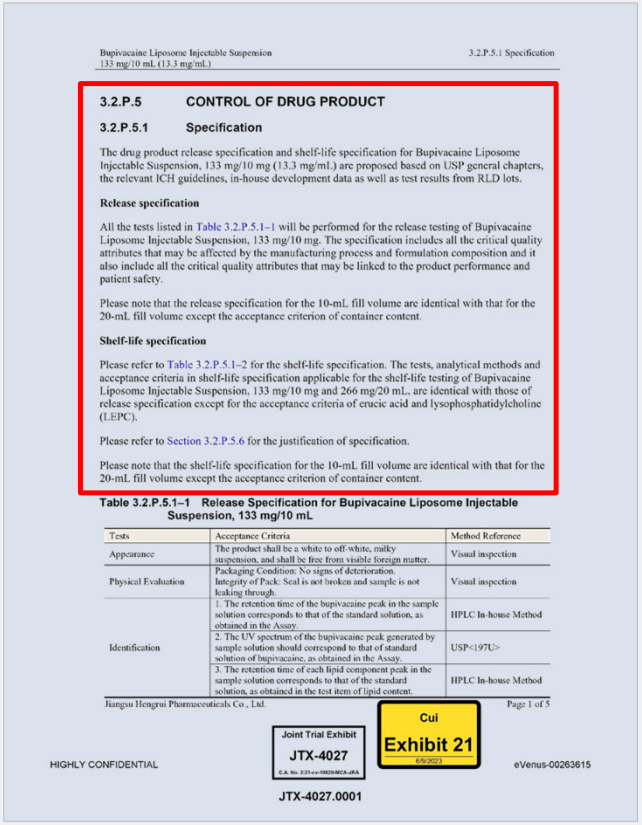
Q. Now, we looked at the erucic acid results, but if we look on page 13 towards the bottom, what was the result of the accelerated stability testing that Jiangsu Hengrui did?

A. There is one of the conclusion given that: "Due to the failure of accelerated stability study, the proposed expiration period for generic drug will be based on real-time data available at the long-term storage condition."

Q. Can you explain what that means?

A. It means they performed accelerated stability study and followed the parameters, one or more parameters failed at this temperature and because of that, they will be based, the shelf life, on real data from storage in refrigeration, the data from 2 to 8 degrees.

Release and Shelf-life Specifications



Bupivacaine Liposome Injectable Suspension 133 mg/10 mL (13.3 mg/mL) 3.2.P.5.1 Specification

3.2.P.5 CONTROL OF DRUG PRODUCT

3.2.P.5.1 Specification

The drug product release specification and shelf-life specification for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg (13.3 mg/mL) are proposed based on USP general chapters, the relevant ICH guidelines, in-house development data as well as test results from RLD lots.

Release specification

All the tests listed in Table 3.2.P.5.1–1 will be performed for the release testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg. The specification includes all the critical quality attributes that may be affected by the manufacturing process and formulation composition and it also include all the critical quality attributes that may be linked to the product performance and patient safety.

Please note that the release specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

Shelf-life specification

Please refer to Table 3.2.P.5.1–2 for the shelf-life specification. The tests, analytical methods and acceptance criteria in shelf-life specification applicable for the shelf-life testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg and 266 mg/20 mL, are identical with those of release specification except for the acceptance criteria of erucic acid and lysophosphatidylcholine (LEPC).

Please refer to Section 3.2.P.5.6 for the justification of specification.

Please note that the shelf-life specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

Table 3.2.P.5.1–1 Release Specification for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL

Tests	Acceptance Criteria	Method Reference
Appearance	The product shall be a white to off-white, milky suspension, and shall be free from visible foreign matter.	Visual inspection
Physical Evaluation	Packaging Condition: No signs of deterioration. Integrity of Pack: Seal is not broken and sample is not leaking through.	Visual inspection
Identification	1. The retention time of the bupivacaine peak in the sample solution corresponds to that of the standard solution, as obtained in the Assay.	HPLC In-house Method
	2. The UV spectrum of the bupivacaine peak generated by sample solution should correspond to that of standard solution of bupivacaine, as obtained in the Assay.	USP<197U>
	3. The retention time of each lipid component peak in the sample solution corresponds to that of the standard solution, as obtained in the test item of lipid content.	HPLC In-house Method

Jiangsu Hengrui Pharmaceuticals Co., Ltd. Page 1 of 5

Joint Trial Exhibit JTX-4027 C.A. No. 2:21-cv-19829-MCA-JRA

Cui Exhibit 21 6/6/2023

HIGHLY CONFIDENTIAL eVenus-00263615

JTX-4027.0001

JTX-4027.1

3.2.P.5 CONTROL OF DRUG PRODUCT

3.2.P.5.1 Specification

The drug product release specification and shelf-life specification for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg (13.3 mg/mL) are proposed based on USP general chapters, the relevant ICH guidelines, in-house development data as well as test results from RLD lots.

Release specification

All the tests listed in Table 3.2.P.5.1–1 will be performed for the release testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg. The specification includes all the critical quality attributes that may be affected by the manufacturing process and formulation composition and it also include all the critical quality attributes that may be linked to the product performance and patient safety.

Please note that the release specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

Shelf-life specification

Please refer to Table 3.2.P.5.1–2 for the shelf-life specification. The tests, analytical methods and acceptance criteria in shelf-life specification applicable for the shelf-life testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg and 266 mg/20 mL, are identical with those of release specification except for the acceptance criteria of erucic acid and lysophosphatidylcholine (LEPC).

Please refer to Section 3.2.P.5.6 for the justification of specification.

Please note that the shelf-life specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

ANDA Products' Shelf-life Based on Long Term (5 °C) Storage Data ONLY

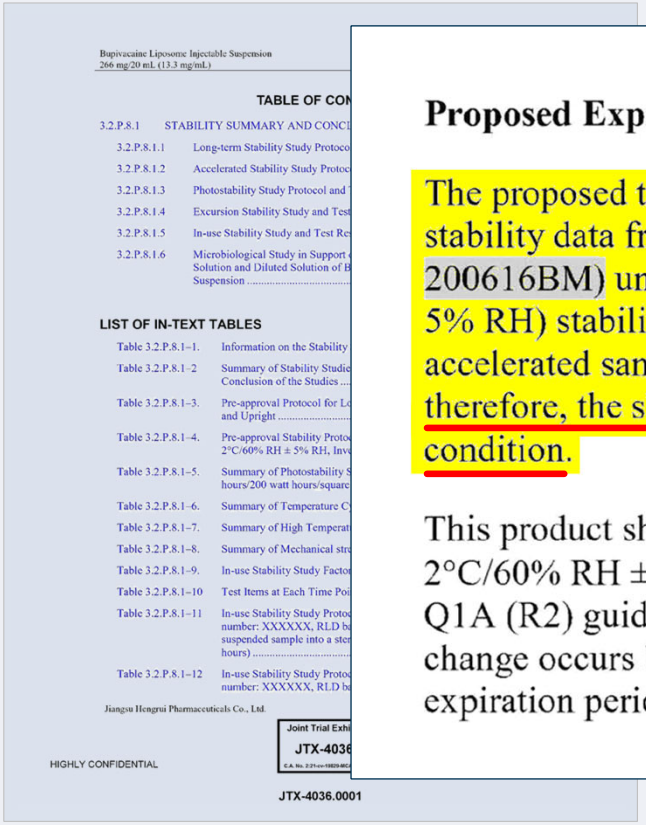

Bupivacaine Liposome Injectable Suspension
266 mg/20 mL (13.3 mg/mL)

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Table 3.2.P.8.1–5. Summary of Photostability S
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Table 3.2.P.8.1–6. Summary of Temperature C
Table 3.2.P.8.1–7. Summary of High Temperat
Table 3.2.P.8.1–8. Summary of Mechanical stu
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Table 3.2.P.8.1–10 Test Items at Each Time Poi
Table 3.2.P.8.1–11 In-use Stability Study Protoc
number: XXXXXX, RLD b
suspended sample into a ster
hours)
Table 3.2.P.8.1–12 In-use Stability Study Protoc
number: XXXXXX, RLD b

Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Joint Trial Exhi
JTX-4036

HIGHLY CONFIDENTIAL

JTX-4036.0001

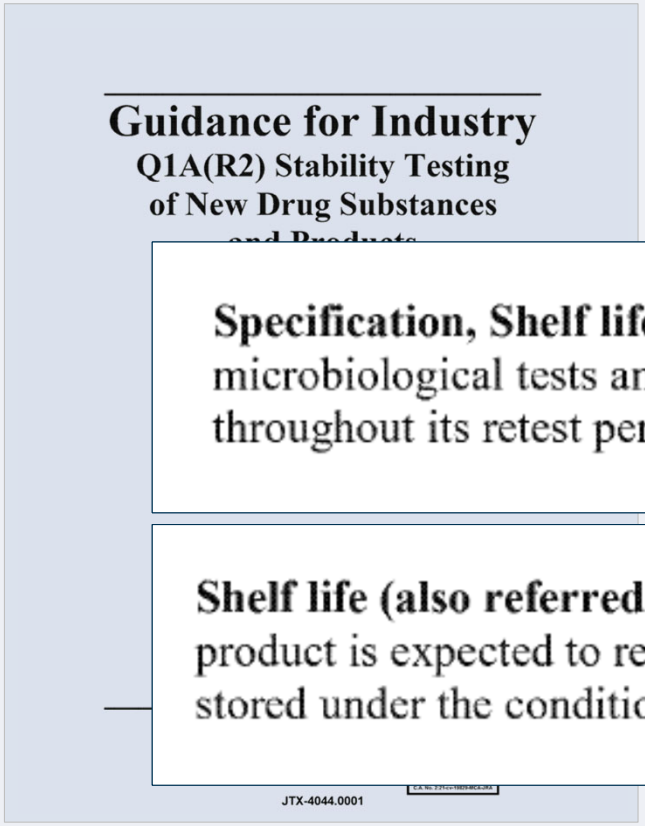
Proposed Expiration Dating Period:

The proposed tentative shelf-life for the generic drug product is 24 months supported by 24 month stability data from three submission batches (batch 191214BL, 191218BM, 191225BM and 200616BM) under long-term storage conditions (2°-8°C). The accelerated (25°C ± 2°C/60% RH ± 5% RH) stability data up to 6 months showed that the encapsulation efficiency results from 6-month accelerated samples were not within acceptable range specified in specification for stability, therefore, the shelf-life will be based on the real time data available for the long-term storage condition.

This product should be stored at refrigerated at 2° to 8°C and accelerated condition is 25°C ± 2°C/60% RH ± 5%, therefore, there is no intermediate storage condition possible. Based on ICH Q1A (R2) guidance, for the drug products intended for storage in a refrigerator, if significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed expiration period should be based on the real-time data available at the long-term storage condition.

JTX-4036.4

Shelf-Life Specification: Long Term Storage Conditions



Specification, Shelf life: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

JTX-4044.22-23

Dr. Schwendeman: No Specification at 25 °C

Dr. Anna Schwendeman

Q. Do you agree with Dr. Karaborni?

A. I disagree.

Q. What's the basis for your disagreement?

A. I believe that none of the seven batches that are made under this ANDA meets the limitation of Claim 7. Sorry, I misspoke. None of the batches meet the limitations of Claim 7. All seven batches.

Q. And –

A. And then also that Jiangsu Hengrui does not have a specification for erucic acid concentration after storage at 25 degrees.

Tr. 392:9-20 (Schwendeman)

Dr. Grigsby: Pacira Has No Specification at 25 °C

Dr. John Grigsby

PACIRA PHARMACEUTICALS, INC.

Q. Dr. Grigsby, you testified on direct that Exparel has stability specifications, correct?

A. Yes, it does.

Q. Specifically, Exparel has stability specifications at 2 to 8 degrees Celsius, right?

A. Correct.

Q. Exparel does not have stability specifications at 25 degrees Celsius, right?

A. That's correct.

Q. Pacira sometimes measures batches at 25 degrees Celsius, right?

A. Correct.

Q. They compare those results to the 5 degree specifications for informational value, right?

A. Yes.

Q. But they don't have a 25 degree Celsius specification, right?

A. Correct.

Tr. 195:23-196:15 (Grigsby)

Pacira Has No Specification at 25 °C

Pacira Pharmaceuticals, Inc. Document: Quality Control Stability Study Protocol
Protocol: PR310 Page 2 of 11

Long-Term Stability Study at 5 ± 3°C and Accelerated Stability Study at 25 ± 2°C
EXPAREL Lots: 129855, 129856, and 129860

STUDY INFORMATION

Product Name: EXPAREL® (bupiv			
Type of Study: Long Term Stabili			
Patheon EXPAREL Lot Number			
129855			
129856	23Mar2020	26Mar2020	Registration
129860	31Mar2020	03Apr2020	Registration

Vials for the accelerated study are pulled and tested using standard test methods per Table 2. Specifications do not apply to the accelerated study. There are only expected result ranges.

DTX-2535.3

① PASS/FAIL criteria not applicable to 25°C accelerated stability SP 04Mar22

① PASS/FAIL criteria not applicable to 25°C accelerated stability SP 04Mar22

① PASS/FAIL criteria not applicable to 25°C accelerated stability SP 04Mar22

DTX-2551.2;
DTX-2552.2;
DTX-2553.2

Dr. Karaborni: Contradicts Pacira

Dr. Sami Kararboni

Q. Dr. Karaborni, were you in court yesterday to hear Dr. Grigsby testify?

A. Yes, I was.

Q. Did you hear him testify – and for the record, this is from the trial transcript day one at page 196.

"QUESTION: But they" – in reference to Pacira – "they don't have a 25 degree Celsius specification, right?"

"ANSWER: Correct."

Do you recall that testimony?

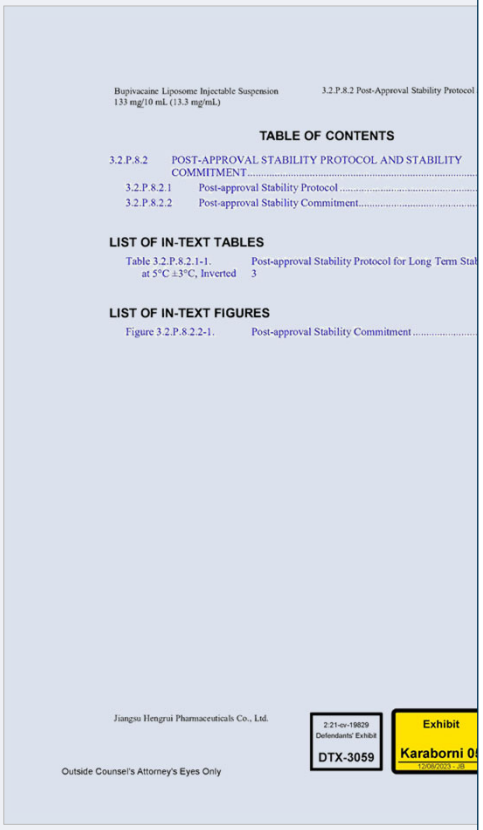
A. I do.

Q. Do you agree with Dr. Grigsby?

A. No, I don't.

Tr. 280:20-281:6 (Karaborni)

Jiangsu Hengrui Has No Commitment to Test Commercial Product at 25 °C



Bupivacaine Liposome Injectable Suspension
133 mg/10 mL (13.3 mg/mL)

3.2.P.8.2 Post-Approval Stability Protocol

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DTX-3059

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Outside Counsel's Attorney's Eyes Only

DTX-3059.6

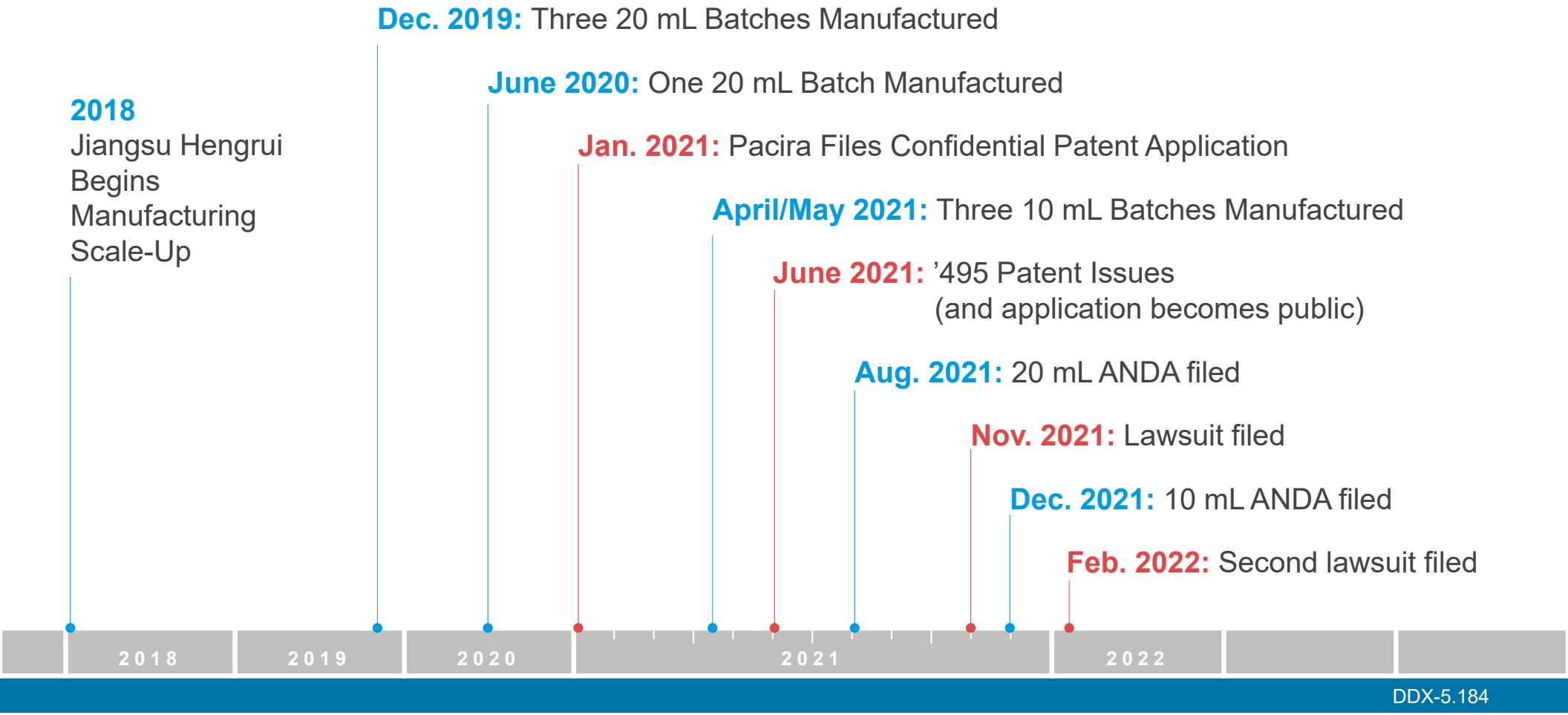
Post-Approval Stability Commitment

Jiangsu Hengrui Pharmaceuticals Co., Ltd. ("Hengrui Pharma") commits that for the three submission batches of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL) described in Section 3.2.P.8.1, the long term stability studies at 2 - 8°C will be continued up to the end of shelf-life.

Therefore, at least one commercial batch of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL) per year (if production is performed that year) will be placed in inverted positions at long term stability condition (2 - 8°C) through the proposed shelf life by Jiangsu Hengrui Pharmaceuticals Co., Ltd. All the stability samples will be packaged in container closure system as approved for marketing.

If any stability sample is found to fail the approved specification during the post-approval long term stability study, Hengrui Pharma will withdraw from the market any batches found to fall outside the approved specifications for the drug product. If Hengrui Pharma has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, Hengrui Pharma will immediately discuss it with the appropriate chemistry team and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product will be reported under 21 CFR 314.81(b)(l)(ii).

Jiangsu Hengrui's Development



DDX-5.184

Conclusion